

# OSTEONECROSIS OF THE JAW BONES IN PATIENTS TREATED WITH BISPHOSPHONATES FOR MULTIPLE MYELOMA

F A VOHRA, M A SHEIKH

## ABSTRACT

Bisphosphonates, particularly those administered through infusions (pamidronate and zoledronate) are commonly used in the therapy of metastatic bone diseases. Although the mechanism is not well understood yet, efficacy of these agents in reducing bone pain, hypercalcemia and skeletal complications has been widely accepted. In the past few years it has been recognized that osteonecrosis of jaw bones can sometimes develop in relation to long term bisphosphonate treatment spontaneously or in relation to dental procedures. We present summaries of six cases of jaw osteonecrosis, all being females and diagnosed with multiple myeloma with a mean age of 62 years, median number of treatment cycles of bisphosphonates given was 44 infusions and the mean time of exposure was 45 months, demonstrating possible relation between osteonecrosis jaw and long term bisphosphonate therapy in order to create awareness of this possible complication within the health care community.

## Key words

Osteonecrosis jaw, Multiple myeloma, Bisphosphonate.

## INTRODUCTION:

Multiple myeloma is a disseminated plasma cell neoplasm, predominantly causing bone lesions. The malignant plasma cells produce defective immunoglobulins (M proteins) and release osteoclast activating factors, which may cause bone resorption and pain.<sup>1</sup> Patients may be asymptomatic or show symptoms of anemia, renal failure, increase in serum calcium and bone lesions. Myeloma cells are malignantly transformed plasma cells that mostly accumulate in the marrow spaces to form a tumour or occasionally collect in tissues and form a mass called plasmacytoma. The chemicals secreted by plasma cells stimulate the osteoclasts into over-activity. The osteoblastic cells cannot keep up and as a result, lytic spots develop and the bone becomes osteoporotic.

Life threatening infectious complications remains a major threat to patients with multiple myeloma.<sup>2</sup> A median survival rate for myeloma patients is two to three years without treatment and bisphosphonate infusion improves the everyday life.<sup>3</sup> Osteonecrosis of jaw bones (ONJ) is usually caused by radiation, infection, necrotizing sialometaplasia<sup>4</sup> or trauma however, its strong relation with bisphosphonate therapy has

been recognized and reported over the last few years.<sup>5-9</sup> American society of clinical oncology has regarded the use of bisphosphonates as standard for multiple myeloma patients<sup>10</sup> and its efficacy in slowing the bone lytic process<sup>1,12</sup> and reducing the complications in myeloma patients<sup>13</sup> i.e. pain, hypercalcaemia and skeletal problems.

Bisphosphonates are analogues of pyrophosphate that fail to metabolise, become localized in bone and inhibit osteoclastic functions. Bisphosphonates bind to exposed bone mineral around osteoclasts, resulting in very high levels in the resorption lacunae. As bisphosphonates are not metabolised, high concentrations of these are maintained within bone for long periods of time. These are well known for their effect on bone turnover,<sup>14</sup> however their exact mechanism of action remains unknown. Some say that they alter osteoclast functions by interacting with intracellular receptors and enzymes<sup>15</sup> they are also known to decrease the osteoclastic activity at bone surface<sup>16</sup> either by inhibiting their recruitment<sup>17</sup> or by decreasing their life span.<sup>18</sup>

Pamidronate (Aredia) and zoledronic acid (Zometa) are commonly used intravenous bisphosphonates for patients with metastatic bone disease and hypercalcemia. Oral bisphosphonates like alendronate are also available but are less potent. Pamidronate infusion is administered over a period of 2 to 24 hours at 90mg dose and zoledronic acid is given in 4mg dose over a span of 15 minutes. It is stated that zoledronic acid is more effective<sup>19</sup> in reducing hypercalcemia and skeletal problems as compared to pamidronate. All of

Correspondence:  
Dr F A Vohra  
University Of Edinburgh  
United Kingdom  
Tel: +44-(0)131-2288039  
Cell no: +44-(0) 07812068513  
fahimvohra@yahoo.com

our patients developed ONJ after being placed on zoledronic acid. They received an average of 20.5 zometa infusions before presentation in oral surgery.

#### CASE REPORT:

The group of patients were referred from Haematology departments of Sandwell District Hospital to Oral Surgery Department Birmingham U.K. due to their oral symptoms. There were six females with a mean age of 62 years (range 43-79 years) having diagnosed for multiple myeloma, previously treated with bisphosphonates including pamidronate. These patients were entered into a Zometa trial due to its efficacy in reducing the bone lesions and symptoms. They received bisphosphonate infusions (Aredia and Zometa) for a average number of 44 (range 24 -67) treatment cycles and the mean duration of exposure to these drugs was 45 months (range 24-68 months).

All the patients had oral symptoms of exposed bone, non healing socket, tooth mobility, pain and facial swelling. Thorough clinical assessment and a strong drug history were suggestive of recently debated bisphosphonate mediated jaw osteonecrosis. We recorded sites and symptoms of ONJ, its relationship with dental extractions and type and duration of bisphosphonates administered (table 1).

Lytic myelomatous lesions in half of the subjects involved the vertebral column, however involvement of ribs, skull and head of femur were also evident on investigations. Only one patient received radiotherapy to back for five days but none to the head and neck region. One of the subjects underwent bone marrow transplant for plasma cell neoplasm. Four patients were added Zometa along with pamidronate for a few months duration whereas two were switched to Zometa infusions only. The range of Zometa infusions was 16 to 25 x 4mg with mean of 19 infusions (table 2). Two patients of the group received cytotoxic drugs (cyclophosphamide, thalidomide) and steroids along with bisphosphonate infusions as part of myeloma therapy.

All the subjects referred to our department came with the complain of jaw pain of which three had visible facial swellings, two having in the mandible, anterior and angle region and one in the maxilla posterior area. Two of them presented with non - healing of extraction sockets and one with necrotic bone both in the maxilla and mandible involving whole of upper anterior and lower right posterior quadrants up to the retromolar pads (Fig 1). Radiographs did show characteristic lytic lesions of multiple myeloma and periodontal ligament widening (Fig 2 ), considered to be as a sequel of bisphosphonate. Biopsy of all patients was performed. Tissues from non healing sockets showed florid lymphoplasmacytic infiltrate. Histopathology of the exposed bony patches revealed abundant purulent material and necrotic bone. Laboratory findings of the patient having soft swelling in the anterior arch were presence of hyperplastic fibroepithelial growth .

Patients were given long term antibiotics to prevent infection (osteomyelitis). Debridement of non healing sockets and exposed areas of bone were also carried out. Subjects were also encouraged towards maintenance of good oral hygiene protocol and regular use of antiseptic mouthwash, were advised. These measures brought substantive improvement to the quality of life of patient and relieved their symptoms to a certain extent if not providing a complete cure.

#### DISCUSSION:

It looks quite obvious from these cases that bisphosphonate therapy contributes significantly in the development of osteonecrosis jaw. The initial studies on this relationship were conducted by Marx<sup>5</sup>, Migliorati<sup>7</sup> and Wang et al.<sup>6</sup> Marx reported 36 patients who developed osteonecrosis jaw both in mandible and maxilla due to bisphosphonate therapy for hypercalcemia.<sup>5</sup>

Wang et al and Migliorati described 3 and 5 cases respectively with almost similar findings.<sup>6,7</sup> Lugassy et al presented 3 myeloma patients who developed osteonecrosis of jawbones with bisphosphonate therapy.<sup>20</sup> Bamias et al reported 17 (6.7%) cases of ONJ out of 252 patients treated with BPT's.<sup>21</sup> The mean number of infusions were 52 and 35 in Lugassy et al and Bamias et al studies respectively, in comparison to 44 mean infusion administered to patients in this case series.

Almost all of the above mentioned studies of osteonecrotic lesions show predominant involvement of mandible. The effect of bisphosphonates on osteoclasts combined with their known antiangiogenic effect i.e. by decreasing the circulating levels of endothelial growth factors, likely to be responsible for the osteonecrosis of the jawbones.<sup>22</sup> Two of our subjects developed ONJ after tooth extraction which is now considered as a risk factor.<sup>5,7,9</sup> This is due to the fact that bone healing is impaired and the socket tissues are exposed to oral flora and external environment making it prone to ONJ. Two patients were given dexamethasone, cyclophosphamide and thalidomide in the early stages of their treatment. It was difficult to find any published reports on the relationship of these drugs and ONJ. However, long term steroid use has been implicated with osteonecrosis of femoral and humeral heads.<sup>6</sup>

Bamias et al concluded that the unwanted osteonecrotic effects due to zoledronic acid alone are higher than pamidronate alone or in combination with zoledronic acid.<sup>21</sup> In our case series ONJ developed when patients were on zometa trial and received a mean number of 20.5 infusions (range 16-25) over a duration of 22 months (range 17-28months). The reason for this is unknown however, a possible explanation is, firstly zoledronic acid has greater antiresorptive effect than pamidronate and secondly its antiangiogenic effect is more established than the later.<sup>21,22</sup>

Recently it was recognized that zoledronic acid produced greater reduction of collagen type I degradation products

**Table 1: Clinical & Management Profile of Patients in This Series**

No.	Age/ Sex	Drugs used in MM Therapy.	Infusion Cycles of BP Given	Signs/Symptoms of ONJ	DXT Radiotherapy
1	62,F	Cyclophosphamide Na, Chlodronate Zoledronic acid	61	Facial pain & swelling, exposed necrotic bone	Only to hip
2	56,F	Cyclophosphamide, Interferon	67	Jaw pain, non healing ext socket UL6. Mobile UL5	Only to shoulder
3	43,F	Na Chlodronate, Zoledronic acid	24	Facial Pain, Swelling & Non healing socket UL6	None
4	68,F	Thalidomide, Allopurinol, Na chlodronate, Zoledronic acid	24	Jaw pain, Mobility LL5, PDL space widening	Only to T6,8,9 Vertebrae
5	62,F	Cyclophosphamide, Pamidronte, Zoledronic acid	58	Jaw pain , Non healing socket LR6	None
6	79,F	Steroids, Melphalan Cyclophosphamide, Pamidronte, Zoledronic acid	28	Facial swelling, lip paresthesia	None

**Table 2: Duration and number of zometa cycles received by patients.**

No	Start of zometa	Onset of symptoms	Zometa stopped	No. of zometa cycles
1	Feb 2003	July 2004	June 2005	25
2	July 2003	May 2005	June 2005	21
3	March 2004	Oct 2004	July 2005	17
4	Jan 2004	July 2005	July 2005	19
5	June 2003	June 2005	June 2005	25
6	Dec 2002	March 2004	April 2004	16

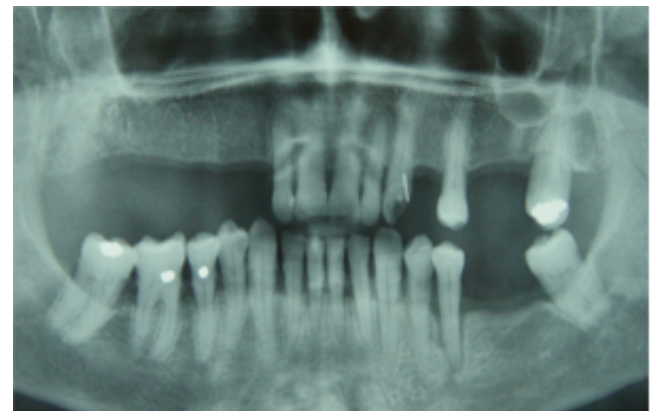


Fig 2 X-ray OPT Showing Widening Of PDL Spaces of Almost All Teeth



Fig 1 Exposed Necrotic Bone at the Anterior of Maxilla due to ONJ

than pamidronate. Bamias et al also concluded that the length of exposure seems to be the most important risk factor in this complication. Bisphosphonates especially zoledronic acid stands as the major risk factor along with other minor factors like extractions, in the development of ONJ.

Management of bisphosphonate related ONJ has always been challenge for oral surgeons as the healing ability is reduced. Surgical debridement of necrotic bone is not always effective as viable bleeding bone at the surgical margins is difficult to achieve.<sup>8</sup> Hyperbaric oxygen use is limited and has not shown significant effect in limiting the progression of disease.<sup>8,21</sup> Discontinuation of zoledronic acid and better dose adjustments of other bisphosphonates are strongly recommended. However, in some cases it was found that the necrotic lesion continued to spread regardless of bisphosphonate cessation.<sup>8</sup>

Use of antibiotics and debridement procedures may be essential to limit the spreading ONJ. Patients should be encouraged towards maintaining good oral hygiene. It is also advised that dental consultation should be arranged prior to bisphosphonate therapy and regular dental check ups taken. The health care community should be well aware of these rare but serious oral effects of bisphosphonates. Careful dental evaluation and any required preventive dental care before starting bisphosphonate therapy should be the first step. The risk of infections or injuries should be minimised by adjusting dentures, avoiding gingival injury with flossing and treating any infections promptly. Avoid tooth extraction and/or any elective jaw surgery if at all possible. Dental implants should be avoided if possible as no evidence is available at present. Preservation of teeth by root canal treatments and crowns are safe. A lot of work needs to be done especially regarding the dose adjustments of bisphosphonates, establishing the risk and predisposing factors need to be unveiled and protocol for the management of ONJ needs to be established.

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