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**BISPHOSPHONATES ASSOCIATED  
OSTEONECROSIS OF THE JAW: A LONG TERM  
FOLLOW UP OF A SERIES OF 35 CASES  
OBSERVED BY GISL AND EVALUATION OF ITS  
FREQUENCY OVER TIME**

Samantha Pozzi, Raffaella Marcheselli, Simona Falorio, Luciano Masini,  
Caterina Stelitano, Antonietta Falcone, Giovanni Quarta, Luisa Ponchio,  
Vincenzo V. Pitini, Stefano Luminari, et al.

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8 **ITS FREQUENCY OVER TIME**  
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43 **Running title:** Follow-up of osteonecrosis of the jaw  
44

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**Abstract:**

**Aims of the study were long term follow-up (FU) of bisphosphonates-associated osteonecrosis of the jaw (ONJ) in 35 cases observed by Gruppo Italiano Studio Linfomi (GISL) between 2002-2005 and the evaluation of its frequency in multiple myeloma patients over time. We asked the centres to up-date cases with ONJ, and to report new cases of ONJ diagnosed between 2006 and 2008. After a median FU of 31 months, 19 patients are alive, 13 died, mainly from progression of the primary disease, and 3 patients are lost to follow-up. Treatment was mainly conservative, however 9 patients underwent surgery. Overall improvement was reported in 13 patients, 11 stabilized and 8 patients progressed. One patient relapsed after dental procedure. ONJ impacted quality of life, causing pain and interfering with the ability to eat. Although the frequency of ONJ in myeloma patients in the period 2006-2008 was slightly increased (3.6% versus 1.9% in 2002-2005), we confirm the rarity of the complication.**

**Running title:** Follow-up of osteonecrosis of the jaw

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3 (... ) Bisphosphonates (BP) related osteonecrosis of the jaw (ONJ) is characterized by an avascular  
4 necrosis of the mandible or maxilla in patients receiving BP and not exposed to radiotherapy of  
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6 head and neck. [1, 2]  
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10 In 2005 Gruppo Italiano Studio Linfomi (GISL) carried out a multicentric retrospective survey [3]  
11 reporting 35 cases of BP-related ONJ in cancer population, diagnosed between 2002 and 2005. In  
12 this new study, we report on long term follow up (FU) of the cases previously described, and the  
13 frequency of ONJ in multiple myeloma (MM) population over time in the same GISL centres.  
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16 For this purpose we asked the GISL centers to update the (... ) evolution of ONJ and the quality of  
17 life of their patients after the diagnosis of ONJ. We also asked to report the number of MM patients  
18 receiving BP treatment in the period January 2006-June 2008, and the new cases of ONJ diagnosed  
19 at each center in the same period in the MM population, the prophylactic measures adopted, and any  
20 change in the schedule of administration of BP.  
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23 The diagnostic criteria utilized in this study were the same applied in our previous study [3] and  
24 included clinical and radiological findings of ONJ, and the exclusion of cancer localization by  
25 biopsy, when performed. ONJ diagnosis was supported by typical radiological findings of  
26 osteonecrosis, sequestrum or lytic lesions with bone sclerosis and was confirmed by a dentist or  
27 maxillofacial surgeon.  
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30 The results showed that after a median FU of 31 months since the diagnosis of ONJ, 3 patients are  
31 lost to FU, 19 are alive while 13 patients died: 12 due to progression of the primary disease and 1 as  
32 a result of infection complicating ONJ. All the patients, except one, suspended BP administration at  
33 diagnosis of ONJ, but no one showed progression of skeletal related events by clinical evaluation.  
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36 The treatment of the ONJ was mainly conservative, based on antibiotic and oral rinses. However 9  
37 patients, with advanced stage, underwent surgery after conservative treatment. The surgery ranged  
38 from curettage (3 patients, all improved), to osteotomy (2 patients; 1 stable, 1 improved),  
39 osteosynthesis (2 cases, both improved) and osteotomy with oromandibular reconstruction with  
40 fibula implant in one case. This patient died after surgery due to sepsis. Another patient received  
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3 surgical treatment, the details of which were not further specified, and ONJ relapsed. The overall  
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5 improvement of ONJ, after conservative and surgical treatment, was observed in 13 patients (12  
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7 patients improved and 1 resolved with healing of the lesion; 41%), while 11 had stable disease  
8  
9 (34%) and 8 patients progressed (25%). The progression of the ONJ was related to the development  
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11 of fistula (4 cases), (...) or local infection (2 patients) and appearance or extension of exposed bone  
12  
13 area. (...)

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17 ONJ reduced the quality of life of many patients, mainly due to pain, requiring pain relief treatment  
18  
19 and interfering with the ability of eating in 15 out of 32 patients.

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22 (...) The new estimated frequency in the MM population is slightly increased compared with the  
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24 previous analysis. In the period 2006-2008, we observed 40 new cases of ONJ, over a population of  
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26 1108 MM patients treated with BP reaching 3.6%, compared with a frequency of 1.9% in 2002-  
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28 2005, that corresponds to 28 cases over a population of 1402 MM patients

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31 **Discussion:** BP-related ONJ is still not a fully understood condition, and pathogenesis and  
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33 cofactors are still a matter of investigation. BP-associated ONJ has been recently defined by the  
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35 American Society of Bone and Mineral Research [4] as a lesion in the maxillofacial area,  
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37 characterized by exposed bone, not healing within 8 weeks, in patients treated with BP not  
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39 receiving local irradiation. However in this definition the pathognomonic feature of the lesion is the  
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41 bone exposure, that in our opinion is a late event, excluding from the diagnosis early stages of the  
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43 disease. In 2005, at the time of our first study, there was no consensus definition of ONJ, and we  
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45 defined BP-related ONJ based on clinical and radiological findings, exclusion of cancer localization  
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47 when biopsy was performed, and confirmation by dentist or maxillofacial surgeon [3]. Exposed  
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49 bone was considered a late manifestation of the phenomenon.

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55 Currently, very few data about long term FU of ONJ are reported in literature [2, 5, 6] and are  
56  
57 summarized in Table 1.

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60 Badros et al. [5] reported data of FU of 97 patients with ONJ from a Greek and US study, relating  
the evolution of ONJ with the evolution of MM. ONJ resolved in 62% of the cases, and no healing

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3 was observed over 9 months in 26% (Table1). Surgery was performed in 36 patients, but no data  
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5 about the outcome of ONJ after surgery are reported. With respect to evolution of MM, more  
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7 frequent relapse of MM was observed in patients with recurrent or non-healing ONJ.  
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10 In another longitudinal FU from a single centre, Mehrotra et al. [6] analyzed the evolution of ONJ  
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12 by stage, showing a better outcome for early stage compared with advanced stages, suggesting that  
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14 early diagnosis and conservative treatment after suspension of BP may improve the evolution of the  
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16 disease (Table1).  
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19 In consideration of the diagnostic criteria applied in our study, the staging system currently used  
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21 cannot be applied. However, after a median FU of 31 months, we observed resolution in just 1  
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23 patient out of 32 (3%), but stabilization or improvement in the majority of the cases (75%). One  
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25 patient out of 32 (3%) relapsed after a dental procedure. The percentage of relapse is very low  
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27 compared with the 12% reported by Badros et al. and it may be related to the fact that all but one of  
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29 our patients suspended BP treatment.  
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33 Surgery, that seems to be a very controversial treatment for ONJ, in our study showed an  
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35 improvement or stabilization of the lesion in 8 out of 9 patients, and we think that it may be  
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37 considered in very advanced stages as already suggested by other authors [2]. In our case series,  
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39 ONJ did not reduce the life expectancy of cancer patients, and death was mainly due to progression  
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41 of the primary disease, although ONJ is not completely without risk, given that 1 death resulted  
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43 from infection associated with surgical intervention of ONJ. We were however not able to make any  
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45 correlation between evolution of ONJ and evolution of the primary disease.  
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50 The real frequency of BP-associated ONJ is not known but has been confirmed to be lower than  
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52 10% in many publications [2, 7, 8]. After the identification of ONJ, the majority of physicians in  
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54 this study decided to discontinue BP administration regardless of bone disease, without reporting  
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56 any progression of skeletal related events, which were clinically evaluated. Almost all the centres  
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58 introduced a dental screening before the start of BP, and the administration of BP has been  
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60 reduced to 2 years of treatment. However the introduction of prophylaxis in our study failed to

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3 reduce the risk of ONJ, as already described in literature [9] and benefits of the prophylaxis might  
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5 be evaluated after a longer FU. In this sequential analysis, the frequency of ONJ was slightly  
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7 increased in the period 2006-2008 compared with the period 2002-2005, but confirms data from  
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9 literature [7, 8] that report the incidence of ONJ in MM population around 3%.

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12 In conclusion: even with the limits of a retrospective and observational study and a small number of  
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14 patients, we can conclude that BP-related ONJ is a rare complication, that doesn't interfere with  
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16 patients survival but reduces the quality of life due to pain and reduced ability of eating. It has a  
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18 variable evolution, but can improve or stabilize in a high percentage of cases (75%), with  
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20 conservative and even surgical treatment in advanced stages, but rarely can heal. In our study, the  
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22 incidence of ONJ is confirmed to be below 5% in MM patients, and stable during this time period,  
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24 despite the introduction of prophylactic measures.  
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29 Identification of the risk factors, better management and knowledge of ONJ evolution, will help  
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31 clinicians to improve the outcome of ONJ and the quality of life of cancer patients.  
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**FIGURES LEGEND**

**Table 1:** Evolution of BP-related ONJ in our case series compared with literature. \*The percentage refers to 32 patients (pts) over 35 (3 patients lost at follow-up).

For Peer Review

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Badros et al. <sup>17</sup> (97 patients)		Mehrotra et al. <sup>18</sup> (94 patients)				Pozzi et al. (32 patients)*
	%		Stage I (26 pts) %	Stage II (45 pts) %	Stage III (23 pts) %	%
<b>not-healed</b>	26	<b>stable</b>	73	47	52	34
<b>resolved</b>	62	<b>improved</b>	19	31	22	41
		<b>worsened</b>	8	22	26	25
<b>recurred</b>	12	<b>relapsed</b>				3

Table 1: Evolution of BP-related ONJ in our case series compared with literature. \*The percentage refers to 32 patients (pts) over 35 (3 patients lost at follow-up).  
246x107mm (96 x 96 DPI)