European Review for Medical and Pharmacological Sciences 2015; 19: 3309-3317

Understanding bisphosphonates and osteonecrosis of the jaw: uses and risks

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Abstract. – OBJECTIVE: Bisphosphonates are chemically stable analogs of pyrophosphate compounds, which have been used to treat multiple disorders of calcium metabolism. Although bisphosphonates have been employed for many years and have demonstrated an excellent safety profile, severe osteonecrosis of the jaw (ONJ) has been described in patients with bone metastases who have been treated with bisphosphonates.

METHODS: In this review we describe the reasons for ONJ and discuss the varying effects of different bisphosphonates on the development of ONJ. Bisphosphonates tend to accumulate in bone, subject to remodeling (such as the jaw) and can affect osteoclast-mediated bone resorption and osteoclast formation, leading to the osteonecrosistic phenomenon.

RESULTS: Risk factors for previously -treated patients include the type of bisphosphonates (amino or non-amino), length of treatment and route of administration, the presence of co-morbidities and/or treatment with immune-suppressing drugs, and the presence of other risk factors in addition to the type of intervention required. In oncological patients currently in treatment withreceiving intravenous bisphosphonates, greater consideration must be taken depending on the length of treatment already undertaken and concomitant therapies. In these patients, a preventive dental surgery visit and examination of the case would be advisable prior to beginning treatment with bisphosphonates.

CONCLUSIONS: Practical approaches in the prevention of ONJ include thorough pre-treatment evaluation and performing any preventative procedures (treat periodontal conditions, extract loose teeth, provide protective and endodontic therapies); initiating amino-bisphosphonates only after any gum tissue damage has healed; establishing a regimented check-up schedule and hygieneic precautions the patient can take; and during bisphosphonate treatment conduct any dental procedures in the least invasive manner during bisphosphonate treatment.

Key Words:
Alendronate, Amino-bisphosphonates, Ibandronate, Osteonecrosis of the jaw, Pamidronate, Risedronate, Zoledronate.

Introduction

Bisphosphonates (BPs) were first synthesized in the 1800s, but it is only in the past 40 years that they have been used to treat disorders of calcium metabolism, such as Paget's disease of bone, tumoral osteolysis, osteoporosis and other conditions marked by increased bone resorption[1]. They are chemically stable analogs of pyrophosphate compounds, which are found widely in nature. Their basic phosphate-carbon-phosphateP-C-P structure allows numerous variants via possible substitutions on the carbon atom or through esterification of the phosphate group[2]. However, although these compounds all present a distinct affinity for hydroxyapatite (OHA), to which they are stably bound, they show notable differences in terms of their biological properties and degree of activity, to the extent that they are generally divided into two classes based on the presence or lack of nitrogen, which confers greater biological potency and different degrees of OHA binding[3]. The presence of nitrogen also lends these compounds a different mechanism of action at the cellular level than compounds without it[3].

Effect of Bisphosphonates on Osteoclasts

Although characterized by a low level of intestinal absorption (0.5%-2%), once they begin circulating in the blood, approximately 50% of BPs are rapidly deposited in bone, and the remainder are equally quickly eliminated, unmetabolized, in urine[3]. Given their clear affinity for OHA, BPs tend to accumulate in bone areas subject to remodeling, because in this phase OHA lacks the sheath of connective tissue and cells that normally covers it[4]. For this reason, BPs tend to be preferentially deposited in areas of bone that are subject to the most significant turnover events, particularly those areas undergoing with inflammation andinflammatory processes consequent to the localized production of numerous

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factors (for example cytokine, prostaglandin E2 and tumor necrosis factor α, all of which) that activate osteoclasts and/or the proliferation of their precursors[5].

Once bound to OHA, BPs are removed only when osteoclasts begin to secrete hydrogen ions and enzymes into the resorption site, producing an acidic-pH medium that makes increases BP availabilityle the BPs, thus, allowing their BP interaction with osteoclast cells, and their phagocytosis with and successive induction of osteoclast the apoptosis of said osteoclasts[6].

Bisphosphonates can affect osteoclast-mediated bone resorption in a variety of ways, that includinge effects on osteoclast recruitment, differentiation, and resorption, and they can induction of induce apoptosis[7]. BPs might also inhibit bone resorption by preventing osteoclast formation, in addition to affecting mature osteoclasts. In contrast to their potential pro-apoptotic effects in osteoclasts, experimental studies suggest that bisphosphonates BPs are able to prevent osteoblast and osteocyte apoptosis *in vitro* and *in vivo*, for example, when induced by glucocorticoids[8,9].

Bisphosphonates and Osteonecrosis of the Jaw (ONJ)

Although BPs have been employed in clinical practice for many years and have demonstrated an excellent safety profile[10], severe ONJ has recently been described in patients with bone metastases who were treated with BPs[11], with cases becoming more frequent as the intravenous use of some particular BPs has become widespread in oncologic practice. This has raised same questions: why might BPs, otherwise so well tolerated and even used to treat some cases of osteonecrosis of the femur and other bone areas, induce ONJ? Furthermore, why do we see only osteonecrosis of in the jaw and not other areas[12]?

In attempting to provide a rational answer, we must first and foremost consider that the jaw and its bones are in a state of continuous remodeling, due to both the mechanical stress to which they are subjected, and to the repair of frequent microfractures. This is why BPs tend to accumulate in the jaw more than in other bone areas, albeit in different ways depending on the physical-chemical characteristics of the specific BPs themselves and the dosage and duration of treatment[13].

In effect, as noted above, one of the distinguishing properties of BPs – utilized in bone scintigraphy by means of labeled technetium – is the distinct tropism for OHA, to which they bind with more or less marked affinity, depending on the chemical structure. Specifically, we know that the degree of affinity decreases appreciably in the following order: zoledronate, pamidronate, alendronate, ibandronate, and risedronate, with and finally clodronate bringing up the rear with much less affinity[14].

It is also important to note that the degree of remodeling of the alveolar ridge is much greater than that involving other skeletal regions; data have shown that in dogs it is approximately 10 times greater than that of the tibia, 5 times that of the mandibular canal and approximately 3.5 times that of the lower jaw[15]. In addition, the trabecular bone is generally characterized by a degree of turnover several (6 to 7) times faster than that of the compact bone, and thus BPs will accumulate more rapidly and also be more quickly eliminated from the trabecular bone upon interruption of treatment[16]. We could say, albeit tentatively, that, compared with a retention time of about 2 years for the trabecular bone, with the compact bone retention may be 15-20 years. As a consequence, we can see that the alveolar bone is a site of particular BP accumulation of BPs. Thus, it should not be surprising that the osteonecrosistic phenomenon tends to manifest itself mainly in alveolar bone, and from there may spread from there to the bone below and to the ramus. Occasionally, sclerosis and even loss of the lamina dura can be observed early on radiographic images, sometimes accompanied by an expansion of the periodontal space[17,18].

In general, BPs are characterized by fast bone tropism; long persistence in bone (several years for amino-derivatives, much less for clodronate); affinity for OHA, varying according to structure; and inhibition of osteoclastic-macrophagic activity.

During the chewing process, forces of compression are distributed to the base of the teeth, and in particular to the lamina dura, which tends to respond to said forces by modifying its remodeling. Where high concentrations of BPs are present, this remodeling is inhibited, with a consequent increase in bone density. In the case of a surgical intervention involving the jaw (extractions, implants), or in the presence of significant periodontal disease or of severe localized inflammation, BPs administered at high doses – as in treatment of bone metastasis – spread into the involved dental area as well. This situation results in an abnormal accumulation of BP in a limited area, reaching concentrations sufficient to inactivate not only osteoclasts, but also osteoblasts and

osteocytes[19]. The lack of osteoclastic resorption of the mineral matrix and the resultant release of bone morphogenic proteins, inhibits the osteoblast formation, and osteons become acellular and necrotic[20].

Role of Different Bisphosphonates on Osteonecrosis of the Jaw

Already at this point, certain differences among various the BPs play important roles, in particular the degree of anti-osteoclastic activity, the bond with plasma proteins and the degree of affinity for the OHA[14]. As we have already mentioned, nitrogen-containing BPs have a much greater degree of activity than non-nitrogen-containing compounds, and inhibit several enzymes in the osteoclastic metabolic pathway, but the major target is farnesyl pyrophosphate synthase (FPPS). Its FPPS action is required for the post-translational modification (prenylation) of small guanosine triphosphatases (GTPases), which regulate a variety of cell processes important for osteoclast function, including cell morphology, cytoskeletal arrangement, membrane ruffling, trafficking of vesicles and apoptosis[21]. In contrast, non-nitrogen-containing BPs are incorporated into non-hydrolysable analogues of ATP and the intracellular accumulation of these metabolites inhibits their function and may cause osteoclast cell death[21].

Among the amino-derivatives, zoledronate is by far the most active compound, and the one with the greatest affinity for OHA, from which it is difficult to separate even when is released under the osteoclasts[21]. Another distinctive factor is the binding of BP to plasma proteins, which regulates the quota of free, and thus available, quota of the compoundsBP. From this point of view as well, zoledronate presents exhibits very limited protein binding – approximately 22%[22], as compared with pamidronate (34%)[23], alendronate (78%)[24] and ibandronate (87%)[16]. Stronger protein binding may contribute to rendering the BPs less available to spread through the osteocyte canaliculi and negatively impact osteocytes[16]. These latter cells, in addition to being important secretors of antibacterial peptides (defensin 1, 2, 3), analogously to osteoblasts, macrophages, dendritic cells and neutrophils[25], are also signals of structural damage and promoters of repair processes[26].

Process of Osteonecrosis

It is thus plausible that in a jaw area undergoing a reparatory inflammatory process, harmful situations may arise due to the invasion of bacteria and actinomycetes with no opposition from defensins nor, most likely, from macrophages, which are partially inactivated by the high BP concentrations of bisphosphonates[27].

It is important to consider the histological aspect of a necrotic area that, although varying from case to case, shows diffuse osteomyelitis, with necrotic osseous coagulum in the presence of widespread infection by both bacteria and by actinomycetes, and purulent destruction[28]. It has been observed that in such an affected area, the not-yet-necrotic bone shows numerous microfractures, most likely due to a repair defect linked to excessive turnover inhibition, in which bacteria has infiltrated unopposed for the reasons described above[27]. The importance of the inhibition of osteoclastic activity in the etiology of osteothe necrosistic phenomenon would also seem to be confirmed by observation of the phenomenon of jaw osteonecrosisONJ following treatment with the recently developed anti-receptor activator NF-kB-ligand (RANKL) antibody[29]. This new product, albeit with a different mechanism than thefrom BPs, is nonetheless a specific inhibitor of the activity of the osteoclasts and its precursors. However, in spite of its potential reliability, this hypothesis lacks a histological demonstration, as available data show the presence of active osteoclasts and areas of resorption within necrotic areas[30].

Thus, osteoclastic inhibition alone does not appear to explain the genesis of the necrotic phenomenon; and in fact, if such were the case, we would be able to find osteonecrosis phenomena in patients affected by osteopetrosis with significantly reduced osteoclastic activity. Instead, we sustain that the *primum movens* is a severe osteomyelitis, which degenerates into necrosis facilitated by the cellular effects of the bisphosphonates BPs and most likely by localized inhibition of mucosal healing, as well as by an initial slowing of the process of microfracture repair, which can allows an abnormal septic and inflammatory phenomenon to readily develop[30]. In fact, we must note that the inflammatory process tends to expand and to infiltrate microfractures, as well as to extending to adjacent areas, determining an interruption of the periosteal blood supply[31]. This phenomenon, of great etiopathological relevance, leads, consequently, to a lack of sustenance to the areas involved and the spread of the necrosistic phenomenon.

While it is clear that the necrosistic phenomenon leads to a dramatic alteration of the bone

structure, it has not yet been ascertained whether this event is determined primarily by over-suppression of turnover, or is instead initially linked to damage to theof soft tissue covering the bone structure[31]. In effect, high BP concentrations of BPs can induce necrosistic phenomena of the skin, the digestive tract and the oral mucous membranes[32]. On this basis, following an extraction or other trauma, there could be an excessive accumulation and release of BPs, which would also influence cellular proliferation in adjacent areas, with damage to the mucous membrane barrier. This damage, and a defect in healing, would generate a sepsis tic process in the bone beneath, sustained by the phenomena described above.

This latter hypothesis has recently garnered widespread credit based on the fact that an exposed bone in the oral cavity is an element that is always present in jaw osteonecrosisONJ. In effect, asserting that the bone lesion is primary and follows an excessive suppression of bone turnover does not explain why the initial signs appear in soft tissues. That nitrogen-containing -bisphosphonatesBPs can sometimes induce esophageal damage or localized necrosis following subcutaneous administration, (or oral ulceration if a tablet is kept in the oral cavity), gives us reason to suggest that tissue damage may actually be the *primum movens* of ONJ[33].

Some *in vitro* studies have shown that a few nitrogen-containing BPs inhibit the proliferation of epithelial cells by inhibiting farnesyl diphosphate synthase (FPPS) in the same way as seenthey act within the osteoclast[34]. On this basis, we might suggest that in the case of prolonged treatment with nitrogen-containing BPs and their consequent considerable localized accumulation, the inflammatory process that originates following from an extraction or other dental trauma, leads to an increase in bone turnover and the localized release of quantities of BP in sufficients quantitysufficient to cause damage to the surrounding soft tissue. This would slow the healing of the wound in the mucous membrane, thus exposing the bone to numerous contaminating agents, with the beginning of aand initiating sepsis tic process unopposed by immune system defense mechanisms, which have been altered by the inhibitory effect of bisphosphonates' BP effect on macrophages and inhibition of defensins release. An important consideration arising from this hypothesis is that any further surgical procedure would be useless, if not outright damaging, in that it would generate a further BP release of BPs as a consequence ofdue to the local inflammatory reaction[35].

This hypothesis, nonetheless, presents a few uncertain points. In effect, we should expect greater incidences of osteonecrosis ONJ following treatment with BPs with less lower bone-binding affinity, like risedronate or ibandronate, as they are more readily released during remodeling[36]. However, it must be noted that these BPs have been used only occasionally in oncology patients, while and experience in cases of osteoporosis is remains still somewhat limited. On the other hand, zoledronate – for which there is ample case documentation[37] – having the greatest affinity with OHA and the least propensity to spread into surrounding tissue, should show a lesser degree of tissue toxicity. To facilitate clarification of this aspect, it may be interesting to evaluate whether localized supply of farnesol (which is normally inhibited by the effect of amino-BPs on FPPS) might be sufficient to inhibit tissue damage.

As we can easily realize, there are numerous factors that intervene in induceing ONJ and can influence the process in various ways. A meaningful and explicative reading is offered by the histological exam which, while potentially variable in individual cases, has nonetheless provided important indications regarding pathogenetic events[38]. We can also find relevant explicative value in the work of Hoefert and Krempien[30] who report that all of the biopsies they performed on oncology patients with ONJ showed active non-specific osteomyelitis with the presence of osseous coagulum, bacteria, and actinomycetes. Also frequently found were newly-formed "woven bone" trabeculae with gaps lacking osteocytes; ischemic bone infarctions were not observed, while the inflammatory tissue contained newly -formed blood vessels. According to the authors, the *primum movens* could be a defect in the oral mucous membrane or in the healing of damaged tissue, followed by a bacterial infection that spreads into the bone through unrepaired microfractures, consequently leading to bone-destroying osteomyelitis. The entire process would be further aggravated by the interruption of blood flow from the periosteum, due to the detachment resulting from the formidable inflammatory process in progress.

To summarize, the observations of Hoefert and Krempien were[30]:

- Microscopic ulceration of the oral mucous membrane with exposure of necrotic bone;

Table I. Some effects induced by high concentrations of bisphosphonates (influenced by the degree of activity and plasma protein binding).

Direct effect of bisphosphonate	Consequence
Inhibition of bone turnover	Unhealed microfractures
Development of infective/inflammatory processes	Release bisphosphonates
Mucous membrane damage	Penetration of bacteria
Increase in enzymes and cytokine release	Inflammatory reaction
Inhibition of macrophages	Decrease of primary immune system defense
Apoptosis of OCs, OBs, osteocytes	Reduction of defensins 1-2-3
	Increase in infective processes
	Severe inflammatory reaction
	Detachment of periosteum
	Vascularization defect
	Necrosis

OBs, osteoblasts; OCs, osteoclasts

- Non-specific osteomyelitis with necrotic osseous coagulum (sometimes sclerotic osteomyelitis);
- Absence of ischemic bone infarctions;
- Inflammatory tissue with numerous blood vessels;
- Presence of bacteria and actinomycetes with invasion of microfractures and purulent destruction;
- Unrepaired microfractures;
- Interruption of blood flow due to detachment of periosteum.

This summary, while leaving a few aspects not fully clarified, may reasonable explain how a necrotic process in the jaw ONJ can occur, and why this event is induced more significantly by certain BPs and concomitant in association with other risk factors.

A great deal of the literature indicates that the most significant number of cases is linked to prolonged treatment with high doses of intravenous zolendronatezoledronate and intravenous pamidronate[11]. These two BPs have particular characteristics, i.e. a much higher affinity for OHA than the other BPs, low protein binding, and elevated macrophage-inhibiting activity, as well as a notable angiogenesis-inhibiting effect, the role of which has not yet been evaluated and would seem to be excluded on the basis of histological findings[30]. Table I offers a schematic picture of how high doses of intravenous BPs can exert an angiogenesis-inhibiting effect. This schema, although indicative, includes a few aspects that are not always constantly chronologically observable, given the complexity of the phenomenon; in fact, the necrotic event may have various origins depending on predisposing factors, but nonetheless arrive at analogous conditions in the end.

Other Factors Affecting Bisphosphonate-Induced Osteonecrosis of the Jaw

Greater incidence of ONJ has been observed in patients affected by multiple myeloma, followed by breast and prostate tumors[39]. The period of development of the phenomenon also varies, with some studies setting it at around 10--18 months over the course of treatment with zoledronate, and 1.5-2.8 years in the case of pamidronate[40]; however, these are approximate values and can vary widely depending on the presence of predisposing factors[40].

Prognostic elements have not yet been validated, although an exposed bone that shows no reparatory process within 3 months after a procedure is considered a negative sign, as is the presence of ulcerations of the oral mucous membrane[31]. A certain correlation has been observed between the degree of remodeling, evaluated by means of the CTX test (C-terminal telopeptide), and risk of ONJ; a higher CTX value (above 150 pg/mlL) is considered an element of reduced risk of ONJ[18]. Various observations can, however, be made regarding the reliability of this parameter, given that it relates to the entire skeleton and not only to the jaw bones, which retain high concentrations of BPs.

Guidelines

As of today, there are still few useful or efficacious guidelines in terms of treatment interventions, which must, however, take into account the seriousness of the case. It can be asserted that,

due to the reduced blood flow that occurs in necrotic areas, systemic therapies offer only modest results, thus the problem must also be dealt with through specific localized treatment targeting the specific bacteria involved. It may be useful to alkalize locally with hydrogen peroxide and sodium -bicarbonate to inhibit the detachment of BPs from OHA, presuming that they can get beneath the active osteoclasts, and carry out a "gentle" cleaning with the aid of a laser[31]. Meticulous oral hygiene and the use of local disinfectants and antifungal agents will be the most -utilized medical aid[41].

Although the ONJ phenomenon has been seen most frequently in oncological patients, due both to concomitant therapies and to high doses of BPs, similar cases have also been found on rare occasions in patients with osteoporosis receiving BP treatment[42]. Such events, however, prove to be less serious, and arise after several years of treatment[42].

With regard to a patients who has been treated with BPs we must, thus, consider various elements must be considered, such as: the type of BPs (amino or non-amino), length of treatment and route of administration, the presence of comorbidities and/or treatment with immune-suppressing drugs, and the presence of other risk factors in addition to the type of intervention required. There is currently no validated approach to the issue, thus common sense is called for, based on knowledge of the pharmacology of the bisphosphonate BP used and on the route of administration, whether oral or intravenous. In the case of osteoporotic patients treated with oral BPs (alendronate, risedronate, ibandronate) for less than three 3 years and without particular risk factors, the possibility of the development of an ONJ following oral surgery would seem extremely low, especially if all standard rules of preventive therapy and meticulous hygiene are followed[43]. The use of clodronate is not usually associated with the phenomenon[44].

As mentioned above, BPs bind stably to hydroxyapatite OHA where they remain for months or years, thus the interruption of BP treatment with the bisphosphonate prior to oral surgery presumably has a more psychological than real effect, unless the interruption is long enough to allow for adequate elimination of the BP from the bone[45]. There is no documentation of regarding the length of such a period for all of the interruption of BP treatment with regard to the jawbone; for example, zoledronate induces a systemic reduction of bone turnover that may continue for many months or years after interruption of treatment[46]. In any case, there are clearly no contraindications to a preventive interruption of 2-3 months, but an interruption of treatment following surgery until the wound is fully healed would be more justified. Patient anamnesis is extremely important, particularly with regard to the existence of pathologies involving the immune system or long-term treatment with immune-suppressing drugs. In these cases, greater prudence is advisable, and more drastic surgery is to be avoided.

In oncological patients currently in treatment with intravenous BPs, greater consideration must be taken depending on the length of treatment already undertaken and concomitant therapies. In these patients, a preventive dental surgery visit and examination of the case would be advisable prior to beginning treatment with BPs. However, even in these types of patients, the use of a bisphosphonate BP following oral surgery or implants or in the presence of periodontal disease, if considered important for greater therapeutic success, is not contraindicated, as long as the patient has not been subjected to prior intravenous BP treatment for long periods.

Suggestions for approaches to take in the presence of evident ONJ are less clear and sometimes contradictory, and the above should, for the moment, serve only as a reference guideline in dealing with such patients who have been treated with BPs.

Finally, we wish to report a practical example to give an idea of the type of risk represented by the use of one of the best-known bisphosphonatesBPs. As is well known, cases of ONJ have been seen particularly in patients with bone metastases in treatedment with perfusions of BPs following dental/oral procedures. Let us instead look instead at the risk factor with regard to patients affected by non-tumoral bone pathologies, such as osteoporosis, who are being treated with oral BPs. We will take as an example two well-known drugs, pamidronate and alendronate.

Pamidronate is used at a dosage of 90 mg intravenously once a month, while alendronate is given orally 70 mg/week or, looking at the monthly total, 280 mg/month. Since alendronate is considered to be about 10 times stronger than pamidronate, the intravenous dose of 90 mg corresponds to about 9-10 mg of alendronate. Therefore, if alendronate were administered intravenously at a dose of 9-10 mg/month, it would

probably have a risk index analogous to that of pamidronate, which has led to cases of osteonecrosis ONJ after around 1-2 years of treatments (average values). As oral alendronate has a bioavailability of about 0.7%[47], the oral dose of 280 mg/month corresponds to about 2 mg/month i.v., and is thus 4-5 times less lower than the pamidronate dosageused for pamidronate. It follows, then, albeit with a certain degree of approximation, that use of oral alendronate would generate the same risks as pamidronate not after 1-2 years, but after 4-10 years of treatment.

It should also be considered that patients with tumors, who have been shown to be particularly susceptible to osteonecrosis ONJ, generally undergo particular treatments that make them much more vulnerable than osteoporotic patients, who usually receive oral treatment.

This example is not intended to suggest that oral treatment with BPs in osteoporotic patients cannot lead to cases of ONJ, in fact the contrary has been demonstrated, but rather aims to give an idea of the risk of inducing osteonecrosis ONJ following an orthodontic procedure in patients treated with BPs, and to provide practical suggestions for the dental surgeon, as follows:

1. Following the initial visit of an oncological patient not yet being treated with BPs, the dental surgeon should carry out a thorough examination of the state of dental health, evaluating the need for preventive procedures that can establish an adequate condition for a period of at least a few months. It may be necessary to treat periodontal conditions or extract loose teeth (3rd-4th degree) and carry out protective and endodontic therapies, as well as thorough dental cleaning.
2. When oral surgery is necessary, the dental surgeon must inform the patient's doctor and/or specialist regarding the need to delay treatment with amino-bisphosphonates BPs until the gum tissue covering the surgical wound has been completely re-established.
3. The dental surgeon must inform the patient regarding hygienic precautions to adopt during treatment with BPs and will set up a calendar of periodic check-ups of the oral cavity, suggesting possible biological or radiological exams.
4. If during the course of treatment for several months with BPs, dental surgery or procedures become necessary, during the of several months' BP treatment, the dental surgeon must evaluate possible risks based on the type of BP taken and the duration of treatment, as well as patient anamnesis and any additional risk factors; if deemed necessary, the procedure must be done in the least invasive way possible, using the least traumatic techniques available, and preceding and following said procedures with adequate antibiotic treatment.

At any rate, it is patent that any guideline suggested cannot take the place of awareness of the ONJ problem and the dental surgeon's experience.

Acknowledgements

The authors would like to thank Simone Boniface of Springer Healthcare Communications who provided medical writing assistance. This assistance was funded by Abiogen Pharma (Pisa).

Conflict of Interest

The Authors declare that they have no conflict of interests.

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