Bisphosphonates and Osteonecrosis of the Jaw

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ABSTRACT

Bisphosphonate-related Osteonecrosis of the Jaw (BRONJ) is a condition which, according to the American Association of Oral and Maxillofacial Surgeons (AAOMS), adversely affects between .8-12percent of the population, a small yet significant amount of adults. Osteonecrosis of the Jaw (ONJ) is characterized by the death of bone and suffering patients present with either a non-healing extraction socket or an exposed jawbone. In general, afflicted patients have been treated with a class of drugs known as the Bisphosphonates (BP). Bisphosphonates were originally developed in order to treat and manage many metastatic diseases of the bone and stabilize bone loss caused by osteoporosis. Recently, oral surgeons have seen many patients with necrotic lesions on the jaw. The common theme between these patients was that they had all received chronic bisphosphonate therapy. This paper will attempt to review current medical literature on this most important topic. To facilitate this, the paper will first delve into the histology and physiology of the bone. Once that is understood, the history of the BP's will be traced: 1) Why they were developed, 2) their early chemical structures, 3) how they

evolved, and 4) what are the current recommendations for patients who are suffering. Reduction of bone vascularity and of the normal remodeling of the bone, and the accumulation of micro-damaged bone, both causes of necrotic lesions to the jaw bone, will be explained and various case studies will be discussed with regard to their diagnoses and treatment/management plans of BRONJ.

INTRODUCTION

There are many conditions which can affect the calcification of bones in humans. These include Paget's disease (Osteitis Deformans), osteoporosis, multiple myeloma, metastatic breast and prostate cancer, and solid tumors of the bones. In all of these diseases, both the quality and quantity of the bone is compromised. This can lead to pain, fracture, spinal cord compression, and hypercalcemia, all of which are associated with a high morbidity (Hotobagyi, GN et al, 1998). The Bisphosphonates, as a class of drugs, were developed to manage these complications and they act by strengthening the bone. They accomplish this through a variety of proposed mechanisms. However, in recent years, much controversy has begun to arise regarding a significant side effect of this therapy-namely- the development of osteonecrosis in the jaw which seems to occur more frequently in those patients receiving Bisphosphonate therapy.

DESCRIPTION OF BONE

Human bone is a complex tissue with functions which run the gamut from the obvious job of providing support and protection for the body's organs, to that of being the body's most important reservoir of calcium, thereby enabling it to maintain calcium homeostasis.

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It is composed of two main components: 1) an organic matrix which is strengthened by 2) firmly attached inorganic calcium safe deposits. The organic component is composed of 95% collagen and ground substance. The collagen matrix is what gives bone its great tensile strength. The ground substance is made up of extracellular components and proteoglycans. The inorganic component is composed of calcium and phosphate combined chemically to form a compound known as hydroxyapatite (Berne et al., 2004). These calcium salts, which are intimately bound to the collagen matric, give bone its extremely high compressive strength (Guyton, 2005).

Bone calcifies in stages. The main cell involved in bone production is the osteoblast. Osteoblasts secrete collagen monomers. These monomers polymerize rapidly and form collagen fibers. The combination of the collagen fibers and the ground substance is called osteoid. Within a few days, the polymerized collagen begins to have calcium salts precipitating on it surface and within a few weeks there are fully hydroxyapatite crystals adhering to the collagen (Guyton, 2005).

Bone is laid down in concentric circles surrounding the blood vessels and nerves within it and which supply it with nourishment. The process begins from the periphery and as the bone is formed, the lumen becomes smaller (Berne et al., 2004). Some osteoblasts become

encased between these concentric layers or lamellae of bone and are then known as osteocytes. As the lumen becomes smaller due to bone deposition, there is the beginning of an encroachment upon the blood vessels and nerves supplying the bone and formation ceases via a negative feedback system. The residual canal through which the vessels and nerves run is called a Haversian canal and each new area of bone deposited in this way is called an osteon. In short, bone is composed of multiple osteons or Haversian systems. As bone ages, it slowly becomes brittle due to the increase in inorganic to organic ratio. The body compensates for the increased ratio by constantly remodeling the bone, i.e. that all through life there needs to be a constant resorption of the old brittle bone and a concomitant deposition of new flexible bone with the ideal ration of components to ensure the proper compressive and tensile strengths of the bone that are needed to support body functions. This task is accomplished by a specialized cell called the osteoclast (OSTEO= bone, KLASTOS= broken –in Greek). This is a large, multinucleated, phagocytic cell (Wheater et al., 2006).

The mechanism of the osteoclastic activity is extremely complex. Briefly, what occurs is as follows. When the time comes for the bone to be resorbed, the osteoclast sends out villus like projections which secrete, 1) Proteolytic enzymes released from lysosomes which have the ability to digest organic material, and 2) Citric and Lactic acid which dissolve the mineral component of the old bone. Additionally, whole fragments of bone salts and collagen are phagocytosed by the villi (Guyton, 2005). Normally, there is equilibrium between deposition and resorption. The osteoclasts are active for about 3 weeks, producing tunnels of about 1 mm in diameter and a few mm in length. This area is then invaded by osteoblasts and new bone formation using new matrix is begun (Guyton, 2005).

As mentioned earlier, bone serves as the body's reservoir of calcium to maintain serum levels. Mobilization of calcium into and out of the bones is mainly regulated by two hormones, each of which is antagonistic to the other. **Parathyroid hormone** (PTH) secreted by the Parathyroid gland causes the rapid dissolution of bone by releasing the calcium and phosphate into the bloodstream. This is accomplished rapidly via direct action but there is also a slower, more sustained phase with the PTH acting to stimulate the production of osteoclasts, which in turn dissolve the bone, releasing the calcium (Guyton 2005). **Calcitonin** on the other hand, is a hormone having the antagonistic effect to PTH. Secreted by the thyroid gland, it serves to decrease the formation of osteoclasts (Wheater et al., 2006) (Guyton, 2005).

With this basic understanding of one histology and physiology, the diseases which affect the bones can now be understood. Once the bone diseases have been clearly outlined, the rationale for the development of the BP drugs can be understood.

DISEASE OF THE BONE

Osteoporosis is the most common metabolic bone disorder in adults. What occurs in this disease is a decreased rate of bone matrix formation. However, the rate of bone mineralization remains normal and steady. In essence what is occurring is that whatever matrix is formed is mineralized normally, but, since there is not enough matrix being formed, the amount of mineralized bone being produced is not keeping up with osteoclastic resorption. This results in a net decrease in volume of mineralized bone per unit volume (Rose and Kaye, 1990). When there is a loss of 30% of bone mass, there is the beginning of pain and increased risks of bone fracture to the individual. The cause of this disease is multifactorial including the natural

decrease in estrogen production in post-menopausal women, which in turn causes a decreased stimulation of the osteoblasts. [In osteoporosis, inhibiting bone resorption by osteoclasts preserves bone density] (Marx et al, 2005).

Cushing's syndrome, another bone disorder, is defined by an increase in the production of corticosteroids which again decreases the osteoblastic function. Any syndrome which decreases the production of protein or increases the catabolism of protein (as examples, diabetes or hyperthyroidism) will result in a generalized osteoporosis (Anderson and Scotti, 1980). Multiple myeloma is a malignant disorder of the plasma cells (Rose and Kaye, 1990). The marrow becomes replaced with abnormal immature plasma cells and they in turn secrete abnormal immunoglobulins which are found in the serum and urine (Rose and Kaye, 1990). Radiographically, there is generalized osteoporosis and there are osteolytic lesions most commonly found in the skull and mandible. These are referred to as 'punched out' lesions. Metastatic prostate and breast cancers invade the bones and the tumor cells produce cytokines which stimulate osteoclasts to resorb the bone (Conte P.F. et al., 1994).

HISTORY OF BISPHOSPHONATES

The bisphosphonate drugs were developed in order to combat many of the diseases of the bone. In the early 1960's, Fleisch demonstrated that the inorganic pyrophosphates (PPi) had the ability to bind to hydroxyapatate crystals in bone and prevent their dissolution by osteoclasts (Fleisch H. et al, 1966). He also found that oral forms of PPi were inactivated by the phosphatases in the stomach. As a result, the organic BP's were developed. The organic BP's were more resistant to the gastric insult and were proven to not only inhibit hydocyapatate dissolution directly by making the hydroxyapatate crystal more resistant to dissolution, but they also prevented bone resorption by inhibiting osteoclastic activity (Gutta and Louis, 2007).

The BP's are similar to the PPi's chemically. The major difference between the two is that the BP's have a carbon atom bridging the phosphate atoms which causes the phosphonate atoms to be more resistant to hydrolysis (Gutta and Louis, 2007). The BP structure looks as follo

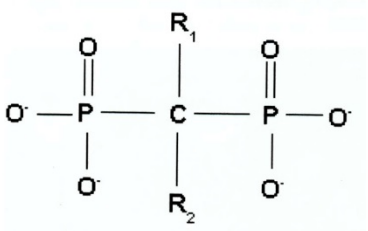

Fig. I. The basic chemical structure for bisphosphonates. (Gutta and Louis, 2007)

The R1 chain always contains a hydroxyl group (-OH) which imparts clinical affinity for bone. The difference in the potency that each BP compound has on bone lies in the alterations of the R2 side chain. The most powerful Bisphosphonates are those with an amino group in the R2 chain of which Zoledronate (Zometa) is the most potent. The following is a list of the currently available Bisphosphonate compounds, their chemical structures, potency and route of administration.

Chemical structure, potency and route of administration of various bisphosphonates

Agent	*R1 side chain*	*R2 side chain*	*Relative potency*	*Route*
Etidronate (Didronel)	OH	$-CH_3$	×1	Oral
Clodronate	Cl	—CL	×10	Oral/IV
Tiludronate (Skelid)	H	-S- ⬡ -Cl	×10	Oral
Pamidronate (Aredia)	OH	$-CH_2-CH_2-NH_2$	×100	IV
Neridronate	OH	$-(CH_2)_6-NH_2$	×100	Oral
Olpadronate	OH	$-(CH_2)_2N(-CH_3)_2$	×1,000	IV
Alendronate (Fosamax)	OH	$-(CH_2)_3-NH_2$	×1,000	Oral
Ibandronate (Boniva)	OH			

MECHANISMS OF ACTION

When the Bisphosphonates are administered, they disappear rapidly from the blood and enter into the bone, remaining there for an extended period of time. Some BP's have half of up to 10 years (Kasting and Francis, 1992)! As mentioned previously, osteoclasts produce acid which dissolves the hydroxyapatite mineral. Since hydroxyapatite absorbs the bisphosphonate and they are incorporated into it structure, as the osteoclast causes the hydroxyapatite dissolution, the bisphosphonates are released and then subsequently absorbed by the osteoclast-thus causing the death of the osteoclast (Marx et al., 2005).

How does this death occur? There are a number of proposed mechanisms of action for the Bisphosphonates. The first generation of Bisphosphonates, such as Clodronate and Etidronate, do not contain any amino groups. After being absorbed by the osteoclast, these Bisphosphonates operate by being metabolized into cytotoxic forms of ATP (Adenosine Triphosphate) which are then incorporated into the osteoclast, causing its apoptosis (Reszka and Rodan, 2003). The more potent Bisphosphonates, i.e. those with amino groups, act by interfering with the production of

FIGURE 6. Photomicrograph of necrotic bone shows empty lacunae. Sequestrum is surrounded by neutrophils and bacterial debris (hema-toxylin and eosin, original magnification x 100). (Ruggiero et al., 2004).

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Additionally, there have been research papers sho to produce a strong osteoclast inhibiting factor (Vi ɔit osteoclast recruitment (Ruggiero et a., 2004).

CASUSES OF OSTEONECROSIS OF THE JAW

The inhibition of the osteoclasts bodes well for the prevention of bone breakdown. However, there many studies showing that concomitant to prevention of bone breakdown, is the development of osteonecrosis. There are many explanations given for this. The first and primary theory is that as the osteoclast function is inhibited, there is a reduction in the normal remodeling of bone. The old bone is not resorbed properly, resulting in an accumulation of micro damaged bone which has less vascularity than healthy bone. Moreover, in a normal, healthy individual, when bone is resorbed by the osteoclasts, the resorption itself stimulates the release of many cytokines and growth factors (Bone Morphogenic proteins- BMP's) which stimulate the osteogenic precursors to differentiate into mature osteoblasts and produce new bone (Storm et al., 1993). When the osteoclasts are inhibited, the release of the cytokines and BMP's is diminished, resulting in a decreased production of new bone (Ruggiero et al., 2004). A second theory given for the reduced vascularity of the bone is that the BP's have been shown to inhibit capillary neoangiogenesis, and to inhibit vascular endothelial growth factor (Marx et al., 2005). Aredia, one of the Bisphosphonate drugs, actually has been shown to decrease bone blood flow in rats (Ruggeiro et al., 2004). Although this second theory sounds attractive, studies have shown that there are many other drugs, such as Thalidomide and alpha 2a- Interferon, which are more potent anti-angiogenic drugs that the Bisphosphonate drugs which do not cause osteonecrosis of the jaw (Marx et al., 2005). Further supports for the osteoclast inhibition theory as being the primary cause of the necrosis, comes from understanding the disease called Osteoporosis, an inherited autosomal dominant trait characterized by the loss of osteoclastic function. These patients present with an identical clinical picture of bisphosphonate- induced exposed bone osteonecrosis in the jaw although angiogenesis is normal (Ibid).

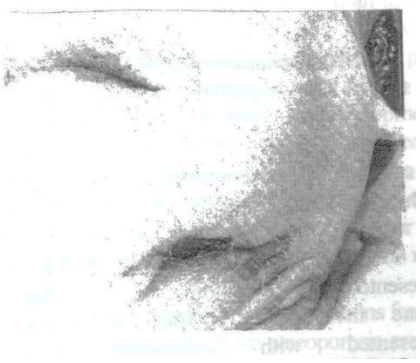


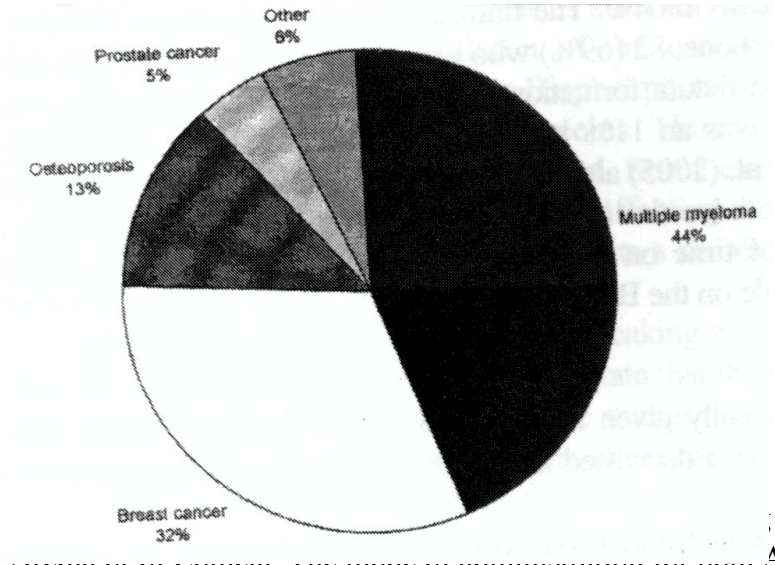
Fig. 2. Chronic orocutaneous fistula with necrosed bone. (Gutta and Louis, 2007)

The development of the osteonecrosis is interestingly noted to be only in the jaws. This is in line with the fact that there is a much greater turnover of one in the jaws due to the presence of teeth and the remodeling of periodontal ligament space. Given this greater turnover, an increased blood supply is needed in the jaw and the consequent lack thereof will cause the necrosis of the jaw (Marx et al., 2005). Osteoclasts live, on average, for about 150 days. (Berne et al., 2004). If after that time no osteoclastic activity occurs, then no BMP, cytokines and other factors are

produced to stimulate new osteoblastic activity. Eventually, the osteon becomes acellular and necrotic, the capillaries become involute and there is a general necrosis of the bone (Marx et al., 2005).

CASE STUDIES

One major study in the ONJ areas was performed by Ruggiero et al (2004), who noticed that there were a growing number of patients at his Oral Surgery Department in the Long Island Jewish Hospital who were being diagnosed with refractory osteomyelitis in the jaw. The typical presentation was a non-healing extraction site progressing to sequestrum formation, exposed bone, localized swelling, and purulent discharge. Up until February of 2001, there had only been one or two patients presented with this condition and when they did, it was always patients who had been receiving radiation therapy. However, not one of these patients had been receiving radiation therapy! Ruggiero's study spanned from February of 2001 to June 2003 and involved 63 patients. There were 45 females and 18 male patients ranging in age from 43 to 89 years of age. The most common oncologic diagnosis was multiple myeloma. The breakdown of the diseases can be seen from the following graph: (Ruggiero et al., 2004)



; infusions of the bisphosphonate Aredia or of Zometa. The mode of administration for both Aredia and Zometa is via IV. [The oral BP's are primarily used to treat osteoporosis (AAOMS, 2006) (Reszka and Rodan, 2003)]. Aredia, which is a first generation Bisphosphonate, is administered over a 2 to 24 hour period every 3 to 4 weeks at a dose of 90 mg. Zometa is administered as a monthly infusion at a dose of 4 mg over 15 minutes (Ruggiero et al., 2004). The duration of therapy ranged from 6 to 48 months.

The breakdown of the medications is seen in the following chart:

Twenty four of these patients (38%) presented ONJ symptoms with maxillary bone involvement. One patient presented symptoms *of both* maxillary and mandibular lesions. Nine of the 63 patients had *no* history of a recent dentoalveolar procedure and yet still presented with exposed and necrotic bone I Microscopic exams of patients' jaws showed necrotic bone, bacterial debris, and granulation tissue. Six of the patients had the signs of osteolysis prior to extraction suggesting that there were lesions prior to any dental procedures.

Another landmark study documenting the exposure of bone in the jaws of patients taking the BP's was begun by Marx in 2003 and involved 36 patients. The present study in 2007, includes those 36 original patients and additional 83 patients. Of the 119 patients followed, 32 (26%) were receiving Aredia, 48 (40.3%) were receiving Zometa and 3 (2.5%) were receiving oral Fosemax. Those patietns on Aredia received 90 mg every 3 to 4 weeks and those on Zometa received 4 mg in the same time interval. Of the patients taking Fosemax, one was taking 10 mg for 6 years and the other 2 had been taking the drug for about 3 years. The mean exposure time until bone became exposed was 14.3 months for Aredia patients, 9 months for patients on Zometa, and 36 months for Fosemax patients. 62 of the patients (52.1%) suffered from multiple myeloma, and 54 (45%) were taking the drugs for bone metastasis from prostate and breast cancer.

Although multiple myeloma is a much rarer disease than cancer and osteoporosis, it is associated with a greater number of ONJ cases because its presence in bone is from the very outset. We see in both studies that multiple myeloma caused an increase in ONJ. The findings include 37 patients (31%) who presented with exposed asymptomatic necrotic bone, 82 (69%) who presented with pain, 28 (23%) with one or more mobile teeth, and 21 (17%) with fistula formation and/or bone exposed through the skin. Subsequent cases were reported where there was an 11% incidence of ONJ in patients taking Zometa (the most powerful of the Bisphosphonates) had twice the incidence of ONJ than patients who were on Aredia. This risk increased as the amount of time on the BP increased- with an estimated 9% increased risk of ONJ for each additional decade on the BP.

MANAGEMENT

Patients who have osteoporosis are usually given the oral form of the BP's (AAOMS, 2006). These forms of drugs are less potent and have a decreased incidence of osteonecrosis associated with them.

The American Association of Oral and Maxillofacial Surgeons (AAOMS), in 2006, issued a position paper on Bisphosphonate Related Osteonecrosis of the Jaw (BRONJ). In it, they noted that it was the Oral Maxillofacial Surgeons who first noticed the correlation between non-healing exposed bone in the jaws and patients who were being treated with Intravenous BP's. The AAOMS, after reviewing the available literature and case studies on the subject, has

concluded that the incidence of BRONJ in the population ranges from .8% to 12% and that with more time and exposure, the figure is likely to rise. The risk factors include the potency of the drug and the duration of time spent on it. The local factors include any insult to the mucosa, such as extractions, implant placements, periapical surgery or periodontal surgery involving osseous injury, which can lead to an ingress of bacteria. Patients who are receiving intravenous BP's and undergo dentoakveolar surgery are seven times more likely to develop BRONJ than patients not having surgery at all. This also applies to patients with inflammatory dental disease (AAOMS, 2006). Novartis, the manufacturer of both Aredia and Zometa has added labeling to their products providing cautionary language in relation to development of osteonecrosis.

Interestingly, the studies quoted earlier show that the mandible has the greatest incidence of developing the osteonecrosis (2:1 over the maxilla). This is due to the mandible having more varied anatomy (e.g. tori, mylohyoid ridge) than the maxilla and the mucosa of the mandible is thinner over those areas. Age is also an important factor to take into consideration. With each decade of age, there is 9% greater risk for BRONJ in patients with multiple myeloma who are on the IV BP's than for those who are not.

The AAOMS recommendations for prevention of BRONJ are as follows:

Patients who have osteoporosis are usually given the oral form of the BP's. These forms of the drug are less potent and have a decreased incidence of osteonecrosis associated with them. However, the risk increases when the duration of therapy exceeds 3 years. If elective dental surgery is planned, it is best to discontinue the oral BP's for 3 months prior to surgery to reduce the risk of developing BRONJ. Patients who are about to initiate BPIV therapy should have all elective surgery performed prior to initiation of therapy and ideally should wait 14-21 days to allow osseous healing and mucosalization. Patients with dentures should be examined for all areas of possible trauma. Patients on IV therapy should avoid procedures that involve osseous injury.

There are three stages in classifying osteonecrosis, as put out by the AAOMS:

Stage 1- Patient has exposed necrotic bone with no evidence of infection. This early stage of osteonecrosis can be managed with oral rinses such as .12% chlorhexidine.

Stage 2- Patient's symptoms include exposed bone with pain and infection. These severer symptoms can be managed with antibiotics, in addition to the oral rinses.

Stage 3- Patient is suffering from exposed necrotic bone, pain and infection, together with either pathologic fracture, extra oral fistula formation or osteolysis. These conditions need to be managed with surgical debridement and resection (Marx et al., 2007).

The potent Bisphosphonate drugs inhibit the mevalonate pathway which produces isoprenoid proteins such as farsenyldiphosphate and geranylgeranyldiphosphate. These proteins are essential to production of the GTP'ases such as Ras, Rho and Rac. These in turn are essential in the production of the cytoskeleton of the osteoclasts and in the integrity of its ruffled border. The future involves designing Bisphosphonate with selective activity against GTP'ases excluding the Rho and Ras groups of proteins. Thus the mevalonate pathways will be spared and the osteoclastic activity will not be affected. Some experimental compounds like NE10790 have that ability to inhibit bone resorption without affecting the osteoclast. Denosumab is a new generation antibody. It is a human 1gG2 molecule that affects a decrease in bone resorption but does not affect the osteoclast (Gutta and Louis, 2007).

After reviewing the case studies and speaking with both an oral surgeon and a general dentist, I feel that the evidence is conclusive enough to state that there is a large risk involved when using Aredia, Zometa, and other Bisphosphonate drugs. The studies presented in this paper and many other studies in this area to date have primarily examined the effects of BP drugs on humans- and not on animal models. Thus, the study results accurately portray the effects of these drugs on humans who have developed ONJ. Obviously, the importance of elucidating the mechanism of this complication is paramount to devising strategies for preventing BRONJ. If the underlying mechanism primarily involves bone remodeling, then eliminating the diseases and conditions that upregulate bone remodeling before starting bisphosphonate therapy can, in some cases, prevent this complication. Although these studies serve to alert dentists and clinicians about the potential complications of bone necrosis in patients receiving bisphosphonate therapy, many questions remain concerning the exact pathogenesis of the process. Further research is needed to elucidate the exact pathogenesis of the process. Further research is needed to elucidate the exact relationship between osteonecrosis and bisphosphonates. The results gathered from these studies and others are conclusive but the mechanism is not conclusive. Knowledge of the factors that incite this condition offers another means of preventing the exposure of bone once bisphosphonate therapy has begun.

CONCLUSION

In conclusion, BRONJ is a condition which is characterized by the death of the bone, with patients presenting with an exposed jawbone or a non-healing extraction socket. The Bisphosphonate drugs, which are taken by cancer patients, multiple myeloma patients, those suffering from osteoporosis, and others, have scientifically been linked to causing these and other symptoms characterized by bone loss, necrotic lesions, and the reduction of bone vascularity. Ongoing studies are searching for possible explanations of the bisphosphonate mechanism, seeking a more efficient recourse of healing ONJ patients as well as an improved quality of life for those suffering from this condition.

SUMMARY

As this paper has shown, BRONJ is a severe condition which adversely affects a small yet significant number of our population. Oral surgeons have recently seen an ever increasing number of patients who suffer from osteonecrosis of the jaw, as a result of chronic bisphosphonate therapy. It is extremely important that all health professionals, especially dentists, oncologists, and oral surgeons, be aware of the possibility that patients being considered for oral surgery or dental implants may perhaps be undergoing BP therapy. Additionally, patients should be informed of the risk of ONJ, so that they will be able to properly evaluate their dental needs and treatment options before starting therapy. BRONJ is a real and painful condition. However, with the current available information and future research on BP mechanisms still being pursued, there is hope that this condition can be successfully managed and perhaps eliminated.

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