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Bisphosphonates and dental implants: Current problems

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Abstract

Osteonecrosis of the jaw has been described in patients taking bisphosphonates after oral surgery procedures, including the placement of dental implants. This review is an update of the relationship between bisphosphonates and dental implants.

Results obtained by different authors are compared, contrasting earlier studies where an improvement in implant osseointegration using bisphosphonates was observed, with ones where statistically significant differences were found, and more recent studies disagreeing with the use of bisphosphonates for causing necrosis of the jaw. The differing results obtained between animal studies and the situation observed in humans may be due to a short medication and follow-up period, as well as to the existence of few research studies where dental implants are placed in the oral cavity.

Currently, dental implants are contraindicated in patients being treated with intravenous bisphosphonates. In 2007, the American Association of Oral and Maxillofacial Surgeons suggested guidelines for patients treated with oral bisphosphonates, based on the clinical situation of the patient and the length of treatment with the drug, and that greater caution prior and subsequent to surgery should be taken for three years after treatment. All patients treated with bisphosphonates must have the risk of possible loss of implants and the risk of suffering a bony necrosis of the operated jaw explained to them, and give their informed consent prior to dental implant surgery.

Key words: Bisphosphonates, dental implants, osteonecrosis of the jaws, oral surgery.

Introduction

Oral bisphosphonates (BP), such as alendronate (ALD), are used in the treatment of patients with osteoporosis or other bone diseases like Paget disease. Intravenous BP are administered to patients with breast cancer, multiple myeloma, bone metastasis and malignant hypercalcemia, to increase survival and quality of life (1). Both oral BP and intravenous BP bond with bone and inhibit osteoclastic bone resorption, osteoclast activity, and induce their apoptosis. The most recent and powerful BP which include nitrogen in their molecule, inhibit tumor proliferation and angiogenesis (1,2).

The main complication observed is osteonecrosis of the jaws (ONJ), which depends on the strength and the half life of the BP. The most powerful is zoledronic acid (ZLD), followed by pamidronate (PAM). ONJ is an adverse reaction to the BF; the main cause for its appearance being dental extractions (70% of ONJ cases) (3-6). The first cases of ONJ were: 36 described by Marx et al. (3) in 2003; 63 by Ruggiero et al. (4) in 2004; and 10 by Bagán et al. (5) in 2005, increasing to 20 in 2006 (6). These side effects had not been detected in previous clinical trials and only after September 2004 did Novartis, along with the FDA, warn about the side effects derived from this medication (7).

The administration of Oral BP, such as ALD, can produce bone exposure after 3 years (8); the consensus for determining the risk limits of ONJ with Oral BP is based on three sources (9): a) a retrospective review of 184 patients medicated with BP and subjected to invasive dental surgery, where the first ONJ was observed three years after medication, increasing in incidence with period of medication (10); b) a follow-up of 224 patients with established ONJ, treated for more than 3 years with oral BP (8); and c) the terminal cross-linking telopeptide type I serum test (CTX), which measures the bone turnover rate. If this value is ≥ 150 pg/ml, the risk of suffering ONJ is null or minimal (these figures were observed in patients medicated for less than 3 years with oral BP); When the values are < 100 pg/ml, the risk of ONJ is increased (values related to patients with more than 3 years oral BP) (11).

Currently, controversy exists in the placement of dental implants in patients treated with BP. A search was made in the Pub-Med database of articles in English and Spanish using the key word "Bisphosphonates", or combinations of "bisphosphonates AND dental implants" and "bisphosphonates AND oral surgery". Clinical trials carried out in animal experimentation were reviewed, as well as articles of clinical cases in humans taking BP in whom dental implants were placed, and those already with implants and medicated with BP.

Animal studies that refer better osseointegration of dental implants with BP.

Table 1 includes 15 clinical trials made in animal experimentation relating dental implants and BP; a third of these studies had a sample size greater than 30. 60% of the authors used ALD, with local application in one third of these studies. For Meraw et al. (12,13) the local application of ALD around the implant improves bone regeneration and implants osseointegration (OI). Similar results have been obtained with the systemic application of BP, such as Narai et al. (14), Tokugawa et al. (15) and Duarte et al. (16), all with subcutaneous ALD, and other authors (17-23) with clodronate (CLD), PAM, ibandronate (IBD) and ZLD.

Meraw et al. (12) observed an increase in early OI with locally applied alendronate, obtaining greater bone-implant contact with smooth surface implants; subsequently they studied the effect of ALD in areas with histological periimplant defects; observing an increase of 5.8% in periimplant bone.

Among studies with subcutaneous alendronate (in 60% of the clinical trials), we find Narai et al. (14), who compared the removal torque of integrated implants in rats with surgically-induced osteoporosis, medicated with ALD, with respect to a healthy control group; they observed a more mature bony quality and a significant increase in removal torque in the cases with ALD with respect to the control group. Tokugawa et al. (15) investigated the action of ALD on bone after placing dental implants in rats with surgically-induced osteoporosis; they suggested that ALD preserved bone-implant contact and the surrounding bone volume, and did not inhibit OI, constituting a preventive treatment against bone loss around the implant surface. Duarte et al. (16) studied the influence of ALD in the health of periimplant bone in rats with surgically-induced osteoporosis; observing greater bone quantity and quality in the rats treated with ALD. Astrand et al. (17) studied the relationship between different doses of ALD and CLD, and the reduction in bone resorption around unstable implants, high doses of both BP were needed to reduce bone resorption in unstable implants.

Besides ALD, other BP have been used. Shibutani et al. (18) studied the effect at systemic level of pamidronate (used in 13.3% of the studies) on bone resorption around implants in animals with periimplantitis. They observed greater periimplant bony loss and a lower bony density in the control group with respect to the group treated with PAM. Yoshinari et al. (19) investigated the bone response in implants treated with an adhered calcium phosphate layer and local PAM; they observed an improvement in osteogenesis around the implants with local PAM.

Kurth et al. (20) studied the influence of dosage in subcutaneous ibandronate treatment (used in 20% of the

Table 1. Clinical animal experimentation trials relating bisphosphonates treatment and dental implants placement.

| Author/year | Age | Gender | Disease | Drug | Via | Length of treatment (years) | Num. Impl. placed | Implants placement | Treatment | Implants with ONJ | Loss of implants |
|------------------------|-----|--------|------------------|----------|---|-----------------------------|-------------------|---------------------------------------|--|-------------------|------------------|
| Starck et al. 95 | 75 | Woman | Osteoporosis | Dis. ETD | -Via oral | 2 | 5 | -Jaw -Anterior region | The Dis. ETD was removed | 5 | 5 |
| Marx et al. 07; case 1 | 72 | Man | Multiple myeloma | ZLD Ac. | - i.v. - 4 mg - 1 injection / month | 5 | 6 | -Maxilla | Ampicillin 2 g with sulbactam 1g every 6h i.v., chlorhexidine 0.12% every 6h. After 10 days oral penicillin 500 mg every 6h and chlorhexidine 0.12% 3 times/day | 6 | 0 |
| Marx et al. 07; case 2 | 58 | Woman | Osteopenia | ALD | - Via oral - 70 mg - 1 tablet/ week | 2 | 10 | -Maxilla | - | 0 | 0 |
| Marx et al. 07; case 3 | 58 | Woman | Osteoporosis | ALD | - Via oral - 10 mg/ day along 1 year - 70 mg/ week over 3 years | 1 | 1 | -Jaw -1 st M left | Piperacillin-tazobactam 4.5 g every 8h 5 days. Debridement. The ALD was removed 10 weeks before. The ALD was changed for raloxifene and the same antibiotics during 1 month | 1 | 0 |
| Wang et al. 07 | 65 | Woman | Osteoporosis | ALD | - Via oral | 5 | 1 | -Maxilla -2 nd PM left. | Penicillin 500 mg every 6h and chlorhexidine 0.12% 3 times/day. Sequestrectomy of the area of exposed necrotic bone in the 36 cases, when the levels of CTX were acceptable. | 1 | 0 |
| Brooks et al. 07 | 62 | Woman | Osteopenia | RSD | - Via oral - 35 mg - 1 dose/ week | 10 | 5 | -Jaw -Anterior region | Drainage, debridement, bone graft with tetracycline (4:1) and collagen membrane. Azithromycin 500 mg every day, 3 days and chlorhexidine 0,12% | 2 | 0 |
| | | | | | | 2,5 | 10 | -Maxilla | Spicules of the necrotic bone were removed, clindamycin 300 mg followed with amoxicillin 500 mg, 10 days. The left sinus was closed by first intention. | 1 | 1 |

*Med. period prior impl.: period of medication prior to implants. ALD: alendronate. PAM: pamidronate. CLD: clodronate. Ac. ZLD: zoledronic acid. IBD: ibandronate. i.m.: intramuscular. i.v.: intravenous. v.o.: via oral s.c.: subcutaneous. PM: premolars. M: molars.

studies) on OI improvement; they observed increased OI for hydroxyapatite implants in rats treated with IBD; they did not find statistically significant differences regarding IBD dosage. Eberhardt et al. (21) evaluated the OI improvement in rats treated with different doses of subcutaneous IBD; they observed greater OI (approximately double) in rats treated with high IBD doses with respect to those treated with lower doses and the control group; subsequently they compared the effect of different IBD doses and the relationship between different types of implants (titanium and with hydroxyapatite) on OI improvement; they observed an improvement in OI for the hydroxyapatite implants associated with high doses of IBD, reducing by half the time necessary to achieve 60% of osseointegrated implant surface.

Bobyn et al. (23) evaluated the relationship between zoledronic acid and bone growth around implants; they observed twice the growth in the group treated with ZLD with respect to the control group.

Other studies (24-26) have focused on the prevention of alveolar bone loss with local (24) and systemic (25-26) application of BP, thus helping to maintain good bone quantity and quality for subsequent placement of dental implants.

Of the 15 clinical trials, an improvement in OI with BP was observed in 80%. In 20%, BP were administered prior to placing dental implants, and of these, the maximum period of BP administration was only 168 days (5.5 months). The maximum follow-up was 90 days in 13.3%; in the remainder the follow-up was shorter. 46.6% used titanium implants, 33.3% included titanium implants and hydroxyapatite implants, 13.3% included hydroxyapatite implants and in one study tantalum implants were used. In 66.7% the location was in long bones and 33.3% in the oral cavity.

Studies in animals and humans without significant differences in dental implant osseointegration with BP

In 20% of the clinical trials, no statistically significant differences were found with respect to OI in implants with or without BP. Denissen et al. (27) found no histological differences in the amount of bone mineralization when relating implants coated or not with local ALD and bone quality; they also found no significant differences (28) in bone repair. Chacon et al. (29) found no relation between oral ALD and improvement in OI; as well as between ALD and periimplant ONJ, affirming that this relationship occurs with etidronate or PAM (table 1).

Jeffcoat MK (30) studied ONJ around dental implants in patients treated with BP (ALD and risedronate); the author compared the success in 50 patients (210 implants) with osteoporosis, 25 treated with BP and 25 in the control group followed for 3 years; there were not statis-

tically significant differences between the two groups. Fugazzotto et al. (31) made a retrospective study observing the relation between the dental implant placement (with or without simultaneous dental extraction) and the appearance of ONJ; 61 patients were treated with BP during a period of 1 to 5 years (an average of 3.3 years); after a follow-up period between 12 to 24 months, there was no ONJ in any of the cases.

Studies in humans against the relation BP - dental implants

Marx et al. (9) presented a series of patients with ONJ caused by BF; three of the cases were related to dental implants, and along with Starck et al. (32), Jeffcoat (30), Wang et al. (33), Brooks et al. (32) and Fugazzotto et al. (31) these are the only reported clinical cases relating periimplant ONJ with BF. Marx et al. (9), Starck et al. (33) and Brooks et al. (34) observed complications such as radiolucent images, exposed and pale alveolar maxillary process, fetid smell, pain, inflammation, infection, candidiasis, fistulas, bone abductions and secondary osteomyelitis, among others.

In the literature, six patients are described with ONJ caused by BP related with dental implants (table 2). Five were women (all over 50 years of age); 3 with osteoporosis and 2 with osteopenia. One patient was treated with zoledronic acid; 3 with alendronate, 1 with etidronate disodium and another with risedronate. In these patients, 44 dental implants were placed in total; 26 when patients had taken BP for less than 3 years and 18 for more than 3 years. Of the first 26, 7 were associated with ONJ and 6 implants were lost (5 in the jaw); of the last 18, 14 suffered ONJ and 4 implants were lost (the 4 located in the jaw).

Comments

In experimental studies in animal treated with BP, an improvement in OI around dental implants has been observed, unlike the results obtained in humans where ONJ may develop. The great inconsistency between the results obtained in animal experimentation studies, and the available data regarding administration in patients, may be due to: a) the short medication and follow-up period with BP in the animal studies, where an improvement in OI was found; and b) the very few studies available where implants were placed in the oral cavity, this being the only location described to date where ONJ has appeared.

In 2007, the American Association of Oral and Maxillofacial Surgeons (35), offered performance guidelines for patients treated with BP. If BP are administered intravenously in cancer patients, the placement of dental implants is contraindicated. If BP are taken orally, three possibilities exist: a) if the patient has been treated for less than 3 years and has no clinical risks, dental im-

Table 2. Patients taking bisphosphonates and treated with dental implants.

| Author/year | Test group | | Control group | Bisphosphonate | Med. period prior impl. | Follow up (days) | No. of implants | Location of implants |
|---------------------|------------|-------|---------------|----------------------|-------------------------|------------------|-----------------|--|
| Meraw et al. 99 | 3 | | 3 | ALD local | - | 28 | 48 | Jaw 2 nd , 3 rd y 4 th PM |
| Meraw et al. 99 | 3 | | 3 | ALD local | - | 28 | 48 | Jaw 2 nd , 3 rd y 4 th PM |
| Denissen et al. 00 | 20 | | 30 | ALD local | - | 90 | 60 | Tibial metaphyses |
| Denissen et al. 00 | 10 | | 5 | ALD local | - | 90 | 100 | Jaw PM |
| Shibutani et al. 01 | 5 | | 5 | PAM i.m. | - | 84 | 20 | Jaw 2 impl. |
| Yoshinari et al. 02 | 5 | | - | PAM local | - | 30 & 84 | 40 | Jaw 4 impl. in M |
| Astrand et al. 02 | A:32 | B: 24 | 56 | ALD s.c. CLD s.c. | - | 37 | 111 | Tibiae |
| Narai et al. 03 | 10 | | 10 | ALD s.c. | - | 25 | 20 | 1 implant in distal metaphysis of the right femur |
| Tokugawa et al. 03 | 18 | | 18 | ALD s.c. | 168 days | 7, 14 & 56 | 36 | Tibial metaphyses |
| Duarte et al. 05 | A:15 | B: 14 | 15 | ALD s.c. | 21 days | 81 | 44 | Tibiae |
| Kurth et al. 05 | A:20 | B:21 | 24 | IBD s.c. | - | 27 | 130 | Femur Medullary canal |
| Eberhardt et al. 05 | A:17 | B:19 | 16 | IBD s.c. | - | 28 | 104 | Femur Medullary canal |
| Bobyn et al. 05 | 7 | | 6 | Ac. ZLD i.v. | - | 45 | 14 | Ulnae Medullary canal |
| Chacon et al. 06 | 10 | | 10 | ALD v.o. | 7 days | 45 | 79 | Femur and tibia |
| Eberhardt et al. 07 | A:22 | B:22 | 44 | IBD s.c. | - | 42 | 176 | Femur Medullary canal |

Num. impl. placed: Number of implants placed. ONJ: Osteonecrosis of the jaw. Dis. ETD: Disodium etidronate. ALD: Alendronate. RSD: Risedronate. ZLD Ac: zoledronic acid. BF: bisphosphonates. PM: premolar. M: molar.

plants can be placed without altering the conventional surgical treatment; b) if the patient has been treated for less than 3 years and is treated jointly with corticoids, BP must be removed 3 months before and not administered again until the bone has completely healed; and c) if the patient has taken BP for more than 3 years it is possible to place dental implants if BP are removed 3 months before surgery and not administered again until the bone has completely healed. All patients treated with BP must be given a full explication of the risks of ONJ and the possibility of implant loss over the long-term for continuing to take BP, and inform consent must be obtained before placing dental implants (32, 35).

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