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Rate of implant failure in patients on antiresorptive drugs: a clinical investigation

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ABSTRACT

Aim The present study is to determine unsuccessful implant cases associated to bisphosphonates and also discuss the etiopathogenesis of medication-related osteonecrosis of the jaw in such patients.
Materials and methods A total of 40 conventional dental implants were placed in 26 patients with a history of antiresorptive drugs therapy. Candidates were asked for any previous history of medicine related osteonecrosis of the jaw (MRONJ). Platelet rich growth factor, allograft and resorbable collagen membrane were used as adjunct measures to the specific sites. RFA (ostell) value was recorded at baseline as well as after sixth month in all cases. The mean follow-up of the study was 42.1 months.
Results Out of a total of 40 implants, 8 failed to integrate. We did not encounter any case of osteonecrosis of jaw but healing was delayed in one patient.
Conclusion The outcome of this study shows that success rate seems to be no different than in patients without a history of bisphosphonate treatment but there may be an added risk of implant failure in patients who are on antiresorptive drugs.

KEYWORDS Antiresorptive drugs; Dental Implants; Implant failure rate; Medicine-related osteonecrosis of jaw (MRONJ).

INTRODUCTION

Advances in surgical and medical intervention and therapeutics are astounding, hence people live longer and their health care needs are also changing globally. As dental professionals, we must understand that medical problems can influence oral health and health care, whilst oral health can influence general health. Medication-related osteonecrosis of the jaw that is linked to the treatment of malignant and non-malignant conditions of the bone continue to receive considerable attention in the scientific literature. Many case reports and studies, albeit for short or relatively short period of time are available in the literature in favor or against the placement of implant in patients taking bisphosphonates or antiresorptive drugs, yet there is no general consensus as to whether it is safe to place implants in such patients or not. The aim of this study is an attempt to determine the bisphosphonate related unsuccessful implant cases.

MATERIALS AND METHODS

This prospective clinical study was conducted at Roshal Implant Training Center, Lokpriya Hospital, Meerut (India) between the year 2012-2017. A total 26 patients were identified with the history of antiresorptive drugs in whom a total of 40 implants were placed. The nature and purpose of the study were explained to the patients and an informed written consent was obtained. Candidates were also asked for any previous history of MRONJ and reviewed by a physician before implant placement.
A strict sterilization protocol was followed and antibiotic prophylaxis was given to all patients.
Authors used minimally invasive technique for extraction of teeth, using rubber band extraction or by the use of periotomes in immediate implant placement cases. Platelet rich growth factor, allograft and resorbable collagen membrane were also used as adjunct measure if

necessary in specific sites. In the postoperative phase all patients were kept on Clindamycin 300 mg, Diclofenac sodium 75 mg, Vitamin E 200 mg for 5 days. The second stage surgery was performed 6 months after implant placement. RFA value was also recorded at baseline as well as after six months in all the cases.

RESULTS

A total of 40 implants were placed in 26 patients who were on oral antiresorptive drugs (except one case who was a postoperative case of central Giant cell granuloma and was on calcitonin nasal spray) between 2012-1017. There were 18 females and 8 males, with mean age of 55.38 years. All patients were immunocompetent with only minor medical co-morbidity. In total six cases of implant failure occurred: in four cases six implants failed to integrate and in the remaing two cases two implants integrated initially but later lost their integration and showed a slow and progressive failure, hence they were eventually removed (Fig. 1, 2). We did not encounter any case of osteonecrosis of the jaw in our study, but healing was delayed in one patient in whom mandibular implant was failed. The mean follow-up was 42.1 months (Table 1).

DISCUSSION

Medication-related osteonecrosis of the jaw is known in the literature by several acronyms but a most recent nomenclature of MRONJ was proposed in AAOMS paper, which should be distinguished from other delayed healing condition according to the following criteria.

1. Current or previous treatment with antiresorptive and/or antiangiogenic agents.
2. Exposed bone that can be probed through an intraoral or extraoral fistula(e) in the maxillofacial region that has persisted for more than 8 weeks.
3. No history of radiation therapy or obvious metastatic disease of the jaw (1).

Many hypotheses have been proposed: being its origin multifactorial, no single hypothesis can explain the pathophysiology of MRONJ, which is continuously modified. Osteoclast activity is tightly regulated by receptor activator of the nuclear factor kappa B(RANK)/RANK ligand (RANKL)/OSTEOPROTEGERIN (OPG) signaling, where an increase RANKL or decrease OPG leads to increased bone resorption. Osteoclast differentiation and function play a dynamic role in bone healing and remodeling at all skeletal sites, but alveolar bone demonstrate a high remodeling rate as compared with other sitw in axial and appendicular skeleton, which may clarify the ONJ predilection for the jaw (2, 3). Since the primary mechanism of bisphosphonates and denosumab is to inhibit osteoclast function by

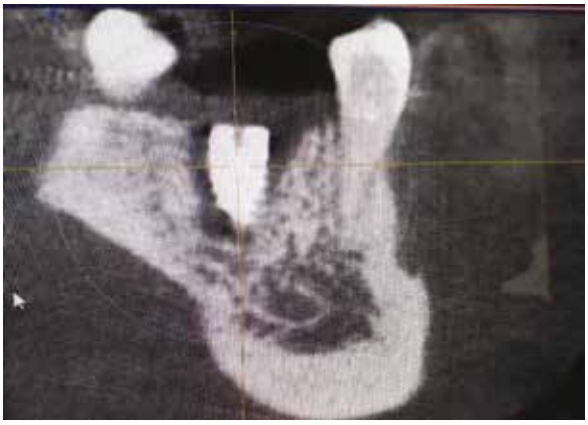

FIG. 1 Peri-implant radiolucency at 3rd month (sagittal plane, CBCT).

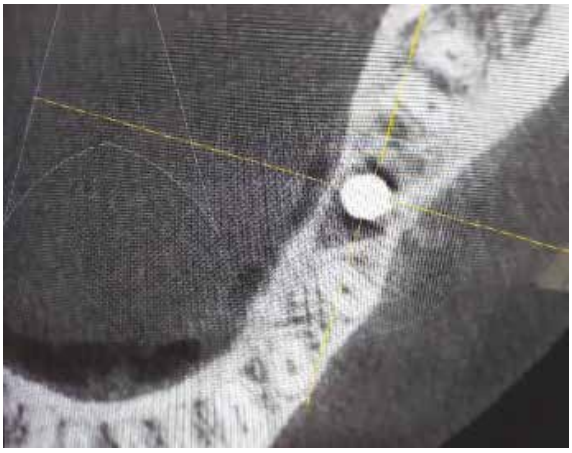

FIG. 2 Peri-implant radiolucency at 3rd month (sagittal plane, CBCT).

different mechanisms, it is not surprising that altered bone remodeling is the leading hypothesis for MRONJ development (4,5). Bisphosphonates bind to exposed hydroxyapatite and incorporate into the bone matrix, where they are retained with half-life of many years (6-8). With the advent of denosumab, which does not integrate into the bone matrix, the half-life is significantly shorter at 32 days maximum and the fast reversibility of its antiresorptive effect diminishes the incidence of MRONJ (9-11).

Enhanced healing of extraction socket and ONJ lesions have been demonstrated with administration of PTH, possibly due to its ability to improve bone homeostasis, by directly stimulating osteoblast function and indirectly increasing osteoclastic bone resorption (12,13). Antiangiogenic drugs like ZA, tyrosine kinase inhibitors, anti-VEGF monoclonal antibodies inhibit tumor invasion and metastases, targeting vascular signaling molecule, and are therefore associated with ONJ development, as bone becomes necrotic without adequate blood supply (14,15). Nitrogen containing bisphosphonates

Age/Sex	Medical status	Disease	Antiresorptive drugs	Total no. of implant placed	Failed implant	R.F.A.		Outcome
						Base-line	At 180 days	
Implant Failed to integrate								
56years/M	ASAII	Osteoporosis	Alendronate for 4 years	12 13 44 46	13 44 46	59 49 55	74 41 59	
52 years/M	ASAII	Osteoporosis	Alendronate for 20 weeks	36	36	59	64	
61 years/M	ASAII	Osteoporosis	Alendronate for 1 year	34 11	11	46	42	
65 years/F	ASAII	Osteoporosis	Alendronate for 1.5 years	26	26	52	49	
Implant integrated initial but Failed later								
57years/F	ASAII	Osteoporosis	Risedronate for 2 years	22	22 (after 13 months)	59	49	
51 years/M	ASAII	Osteoporosis	Alendronate for 1 year	11	11 (after 6 months)	62	51	
Implant integrated successfully								
50years/F	ASAII	Osteoporosis	Alendronate for 1 year	16		49	64	Follow up 56th months
67years/F	ASAII (HbA1C-6)	Osteoporosis	Alendronate for more than 10 months	25 26		59 49	74 71	Follow up 42th months
50years/F	ASAII	Osteoporosis	Alendronate for 2 years	22		56	94	Follow up 60th months
67year/F	ASAII	Osteoporosis	Risedronate for 1 year	16		62	79	Follow up 33th months
49years/F	ASAII	Osteoporosis	Alendronate for 1 year	36		75	79	Follow up 25th months
48years/F	ASAII	Osteoporosis	Alendronate for more than 5 years	36		62	79	Follow up 57th months
55years/M	ASAII (HbA1C-6)	Osteoporosis	Alendronate for 2 years	37 46		71 59	95 85	Follow up 49th months
58years/F	ASAII (HbA1C-5.5)	Osteoporosis	Alendronate for 4 years	14		59	74	Follow up 40th months
35years/F	ASAII (Intralesional steroid)	Hyperparath-yroidism	Calcitonin for more than 10 weeks	11		75	95	Follow up 38th months
52years/M	ASAII	Osteoporosis	Alendronate for more than 5 years	16,15 27,26		64,72 59,65	85,95 74,79	Follow up 52th months
54 years/M	ASAII	Osteoporosis	Alendronate for more than 2 years	31	62	76		Follow uo 48th month
64years/F	ASAII	Osteoporosis	Risedronate for 1 years	36	56	78		Follow up 55th month
60 years/M	ASAII	Osteoporosis	Alendronate for 5 years	46	75	94		Follow up of 38th month
49 years/F	ASAII	Osteoporosis	Alendronate for 2 years	46, 47, 35, 36	49, 63, 68,72	79, 88, 72, 95		Follow up of 44th month
62years/F	ASAII	Osteoporosis	Alendronate for 6 months	26	72	88		Follow up of 24 months
60 years/F	ASAII	Osteoporosis	Alendronate for 2 years	47	69	84		Follow up of 26 months
57 years/F	ASAII	Osteoporosis	Alendronate for 4 years	26	58	77		Follow up of 30th month
48 years/F	ASAII	Osteoporosis	Alendronate for 1 year	24	64	92		Follow up of 44 months
55 years/F	ASAII	Osteoporosis	Alendronate for 3 years	26,16	70, 66	88, 82		Follow up of 32 months
58 years/F	ASAII	Osteoporosis	Alendronate for 6 months	44, 45	66, 72	78, 82		Follow up of 49th months

TABLE 1 Demographic data and treatment outcomes of the sample.

induce apoptosis or decrease proliferation of cervical, prostate, and oral epithelial cells *in vitro* (16-18). Tumor pathogenesis is often associated with an impaired immune function, and animal studies have implicated immune deficiency in the development of ONJ. Hence soft tissue toxicity by bisphosphonates and immune function dysfunction could also be a possible hypothesis of ONJ. However, antiresorptive drugs alone do not cause ONJ until combined with trauma, injudicious tooth extraction, inflammation and infection in immunocompetent patients. Osseointegration in dental peri-implant area involves three phases, the first is osteoconduction, which relies on the recruitment and migration of osteogenic cells to the implant surface. The second healing phase is the development of new bone at the intersection between the preexisting bone and implant. The first two phases result in contact osteogenesis over the implant surface, while the third phase is bone remodeling, which basically involves regeneration of the bone and its contact to the implant surface. Bisphosphonates affect osteoclastic differentiation and hence bone remodeling. When alveolar bone demonstrates increased remodeling rate, implant placement in such patients can show a marked delay in bone healing and thus increased potential for loss of integration. The recent American Association of Oral and Maxillofacial Surgeons position paper on MRONJ recommends avoiding the placement in patients with MRONJ and in oncological patients receiving I/V antiresorptive or antiangiogenic medications. The rate of ONJ is greater in patients receiving I/V bisphosphonates and has been calculated as occurring in one every 11 to 15 extractions (19,20). Dentoalveolar surgery is the most common risk factor, with tooth extraction as the most common event ranging from 52-61%. Risk factors for MRONJ are medications in cancer patients (0.6-7%) (21,22) and in osteoporosis (0.04 – 0.2%) (23,24), local factors like tooth extraction (0.5%) (25), anatomic factors (mandible 73%, maxilla 22.5%, both jaw 4.5%) (26) with increased risk for denture wearers (27), concomitant oral diseases (periodontal or periapical) with a risk of 50% (28), comorbid conditions like anemia (Hb<10g/dl) and diabetes (29). Despite the evidence of the risk of surgery in patients treated with antiresorptive medication, the necessity to perform surgery does exist. The average survival of implants varied from 65.3% to 97% in smokers and in non-smokers from 82.7% to 97% in the follow up cases over 5 years (30). We encountered a success rate of 80% in the present study with an average follow up of 42.1 months, without any case of osteonecrosis of the jaw. Demarosi also stated in his study that oral bisphosphonates did not appear to significantly affect implant success (31). However minimally invasive surgical techniques (Nd-YAG) and adjunctive therapies (PRGF, PTH) that favor optimum healing of bone and soft tissue decrease the risk of ORN and increase success rate of dental implant. In the present study the authors used rubber band extraction technique in one case which was originally described for hemophilic patients while in second case periotome was used for atraumatic extraction. In both cases of immediate implant placement, author focused on primary closure of socket wound after placement of PRGF, bone graft and barrier membrane. Since free bisphosphonates within the serum is usually at extremely low levels 2 months after the last dose of an oral bisphosphonate, a two-month drug free period should be adequate before an invasive dental procedure or until the surgical site heals with mature mucosal coverage after implant placement. Hence, patients on oral bisphosphonates may undergo all types of dentoalveolar surgery, including implant placement, as long as the necessary precautions (bisphosphonate discontinuation, antibiotic coverage, meticulous oral hygiene) are taken (32).

CONCLUSION

Though outcome of this study showing that success rate seems to be no different than in patients without a history of bisphosphonate treatment, there may be an added risk of failure of implant in patients who are on antiresorptive drugs. Clinicians should be aware of the importance of a thorough medical history, in particular in case of bisphosphonates. With proper medical advice, modification in implant placement and salvage techniques, success rate can be improved as conventional techniques are likely to fail in such patients. We recommend for large sample size, long term studies to determine the success rate of implant in patients exposed to antiresorptive drugs.

Conflict of interests

The authors declare that they have no conflict of interests.

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REFERENCES

1. Ruggiero SL, Dodson TB, Fantasia J, Goodday R, Aghaloo T, Mehrotra B et al. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw—2014 update. J Oral Maxillofacial Surgery 2014 Oct 1;72:1938-56.
2. Reinwald S, Burr D. Review of nonprimate, large animal models for osteoporosis research. J Bone Mineral Research 2008 Sep;23(9):1353-68.
3. Huja SS, Fernandez SA, Hill KJ, Li Y. Remodeling dynamics in the alveolar

process in skeletally mature dogs. The Anatomical Record Part A: Discoveries in Molecular, Cellular, and Evolutionary Biology: An Official Publication of the American Association of Anatomists. 2006 Dec;288(12):1243-9.
4. Kimmel DB. Mechanism of action, pharmacokinetic and pharmacodynamic profile, and clinical applications of nitrogen-containing bisphosphonates. J Dental Research 2007 Nov;86(11):1022-33.
5. Baron R, Ferrari S, Russell RG. Denosumab and bisphosphonates: different mechanisms of action and effects. Bone 2011 Apr 1;48(4):677-92.
6. Rogers MJ, Gordon S, Benford HL, Coxon FP, Luckman SP, Monkkonen J et al. Cellular and molecular mechanisms of action of bisphosphonates. Cancer: Interdisciplinary International J American Cancer Society 2000 Jun 15;88(S12):2961-78.
7. Sato M, Grasser W, Endo N, Akins R, Simmons H, Thompson DD et al. Bisphosphonate action. Alendronate localization in rat bone and effects on osteoclast ultrastructure. J Clinical Investigation 1991 Dec 1;88(6):2095-105.
8. Shinoda H, Adamek G, Felix R, Fleisch H, Schenk R, Hagan P. Structure-activity relationships of various bisphosphonates. Calcified tissue international 1983 Dec 1;35(1):87-99.
9. Lewiecki EM. Denosumab: an investigational drug for the management of postmenopausal osteoporosis. Biologics: targets & therapy 2008 Dec;2(4):645.
10. Lewiecki EM. Denosumab update. Current opinion in rheumatology 2009 Jul 1;21(4):369-73.
11. Silva I, Branco J. Denosumab: recent update in postmenopausal osteoporosis. Acta Reumatologica Portuguesa 2012;37(4):302-13.
12. Kuroshima S, Kovacic BL, Kozloff KM, McCauley LK, Yamashita J. Intra-oral PTH administration promotes tooth extraction socket healing. J Dental Research 2013 Jun;92(6):553-9.
13. Kuroshima S, Entezami P, McCauley LK, Yamashita J. Early effects of parathyroid hormone on bisphosphonate/steroid-associated compromised osseous wound healing. Osteoporosis International 2014 Mar 1;25(3):1141-50.
14. Wood J, Bonjean K, Ruetz S, Bellahcène A, Devy L, Foidart JM et al. Novel antiangiogenic effects of the bisphosphonate compound zoledronic acid. J Pharmacology and Experimental Therapeutics 2002 Sep 1;302(3):1055-61.
15. Bezzi M, Hasmim M, Bieler G, Dormond O, Rüegg C. Zoledronate sensitizes endothelial cells to tumor necrosis factor-induced programmed cell death evidence for the suppression of sustained activation of focal adhesion kinase and protein kinasE B/Akt. J Biological Chemistry 2003 Oct 31;278(44):43603-14.
16. Reid IR, Bolland MJ, Grey AB. Is bisphosphonate-associated osteonecrosis of the jaw caused by soft tissue toxicity? Bone 2007;41:318
17. Lin JH. Bisphosphonates: a review of their pharmacokinetic properties. Bone 1996 Feb 1;18(2):75-85.
18. Giraudo E, Inoue M, Hanahan D. An amino-bisphosphonate targets MMP-9-expressing macrophages and angiogenesis to impair cervical carcinogenesis.J Clin Invest 2004;114:623.
19. Mavrokokki A, Cheng A, Stein B, Hawker P. The nature and frequency of bisphosphonate associated osteonecrosis of the jaws in Australia. J Oral Maxillofac Surg 65:415, 2007.
20. Lo JC, O'Ryan F: Predicting the risk of osteonecrosis with bisphosphonate exposure (PROBE) study. Kaiser Permanente Northern California Quarterly Newsletter 10:1, 2007.
21. Gnant M, Mlineritsch B, Stoeger H, Luschin-Ebengreuth G, Knauer M, Moik M et al. Zoledronic acid combined with adjuvant endocrine therapy of tamoxifen versus anastrozol plus ovarian function suppression in premenopausal early breast cancer: final analysis of the Austrian Breast and Colorectal Cancer Study Group Trial 12. Annals of Oncology 2015; 26:313-20.
22. Chiang PH, Wang HC, Lai YL, Chen SC, Yen-Hwa W, Kok CK et al. Zoledronic acid treatment for cancerous bone metastases: a phase IV study in Taiwan. J Cancer Research Therapeutics 2013 Oct 1;9(4):653.
23. Papapoulos S, Chapurlat R, Libanati C, Brandi ML, Brown JP, Czerwiński E et al. Five years of denosumab exposure in women with postmenopausal osteoporosis: results from the first two years of the FREEDOM extension. J Bone Mineral Research 2012 Mar;27(3):694-701.
24. Bone HG, Chapurlat R, Brandi ML, Brown JP, Czerwiński E, Krieg MA et al. The effect of three or six years of denosumab exposure in women with postmenopausal osteoporosis: results from the FREEDOM extension. J Clinical Endocrinology Metabolism 2013 Nov 1;98(11):4483-92.
25. Kunchur R, Need A, Hughes T, Goss A. Clinical investigation of C-terminal cross-linking telopeptide test in prevention and management of bisphosphonate-associated osteonecrosis of the jaws. J Oral and Maxillofacial Surg 2009 Jun 1;67(6):1167-73.
26. Saad F, Brown JE, Van Poznak C, Ibrahim T, Stemmer SM, Stopeck AT et al. Incidence, risk factors, and outcomes of osteonecrosis of the jaw: integrated analysis from three blinded active-controlled phase III trials in cancer patients with bone metastases. Annals Oncology 2011; 23:1341.
27. Kyrgidis A, Vahtsevanos K, Koloutsos G, Andreadis C, Boukovinas I, Teleioudis Z et al. Bisphosphonate-related osteonecrosis of the jaws: a case-control study of risk factors in breast cancer patients. J Clin Oncol 2008 Oct 1;26(28):4634-8.
28. Yamazaki T, Yamori M, Ishizaki T, Asai K, Goto K, Takahashi K et al. Increased incidence of osteonecrosis of the jaw after tooth extraction in patients treated with bisphosphonates: a cohort study. Int J Oral Maxillofacial Surgery 2012 Nov 1;41(11):1397-403.
29. Borromeo GL, Brand C, Clement JG, McCullough M, Crighton L, Hepworth G et al. A large case-control study reveals a positive association between bisphosphonate use and delayed dental healing and osteonecrosis of the jaw. J Bone Mineral Research 2014 Jun;29(6):1363-8.
30. Haas R, Haimbock W, Mailath G, Watzek G. The relationship of smoking on peri-implant tissue: a retrospective study. J Prosthet Dent 1996;76:592–6.
31. Demarosi F, Carrassi A, Leghissa GC. Dental implant treatment in oral bisphosphonates patients using a drug holiday protocol: a prospective study. J Osseointegr 2010 Oct 30;2(3):73-8.
32. Tripodakis AP, Kamperos G, Nikitakis N, Sklavounou-Andrikopoulou A. Implant therapy on patients treated with oral bisphosphonates. J Osseointegr 2012 Mar 30;4(1):9-14.