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 2012-2017. 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 remaining 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 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
Implant failure in patients on antiresorptive drugs

**TABLE 1** Demographic data and treatment outcomes of the sample.

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