Bisphosphonate Associated Osteonecrosis of the Jaw; Similarities and Differences in Oncologic and Non-Oncologic Patients

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Since their introduction to clinical practice more than three decades ago, Bisphosphonates (BP) have been increasingly used for an array of skeletal disorders. BP are synthetic analogues of the naturally occurring pyrophosphate with high affinity for calcium crystals, which allows this pyrophosphate to bind hydroxyapatite of bone and inhibit osteoclast – mediated bone resorption. This provided the rationale for their use as a skeletal protector of cancer mediated cytokine induced hypercalcaemia and in various malignancies, such as multiple myeloma and solid tumors with bone metastasis. In the last decade, BP have been increasingly used to treat bone loss occurring in patients with non-neoplastic disease. The most common clinical condition for which BP therapy is used is osteoporosis, a skeletal condition characterized by compromised bone strength resulting in an increased risk of fracture. Osteoporosis is a clinically heterogeneous disease with several causes, including hormone loss (Postmenopausal and androgen-deprivation), iatrogenic (Glucocorticoid induced and transplant related), physical (immobility), and genetic conditions.

Although a good safety profile has been reported, these drugs might cause mild and transient adverse events, such, as bone pain, pyrexia, anemia, nausea, gastroesophagitis, and dyspnea. Occasionally, acute renal failure, atrial fibrillation, and esophageal carcinoma, mainly occurring in patients on long-term BP therapy, have been reported. Among potential adverse clinical events associated with the use of BP, none has received greater attention than Osteonecrosis of the Jaw (ONJ). In 2003, the first reports describing ONJ in patients receiving BP were published. Majority of ONJ cases (94%) have been reported in patients receiving high doses of Intravenous (iv)BP (primarily zolendronic acid and pamidronate) for oncologic conditions. Whereas the incidence of ONJ is estimated to be 1 to 10 per 100 oncology patients, the risk of ONJ appears to be substantially lower among patients receiving oral BP therapy for osteoporosis, with an estimated incidence of approximately 1 in 10,000 to 1 in 100,000 patient treatment years. A comprehensive literature search for relevant studies on BP associated ONJ was carried out and papers published before Feb. 2008 were reviewed. This systematic review indicates that high – dose IV BP use in the oncology population is associated with an increased risk of ONJ that appears to be dependent on dose and duration of therapy. A similar link has not been confirmed with lower – dose BP therapy in the osteoporosis population. No cases of ONJ were reported in randomized controlled trials of alendronate, risedronate, zoledronate, and ibandronate in non – malignant skeletal disease that collectively included more than 60,000 patients treated for at least two years. Based on in a relatively large cohort of twenty four non–neoplastic patients of BP–induced ONJ a more recent study has pointed out several clinical symptoms of ONJ appear to be similar in neoplastic and non–neoplastic BP–treated patients, including pain, bone exposure, and purulent secretion. However, more severe lesions such as sinus involvement, mandible paresthesia, discontinuation of the inferior mandible border, or cutaneous fistulae, which are frequently detected in neoplastic patients, were not observed in this series of non-oncologic cases, thus supporting a possibly more indolent clinical course of ONJ in non–neoplastic patients. No major co morbidities were ascertained in this series of non-oncolalthough three patients were taking low–dose steroid therapy for SLE and low–dose immunosuppressant agents for RA. respectively. The study concluded that synergistic effects of co morbidity factors in the pathogenesis and prognosis of ONJ require further investigation in larger series of patients.

In the current issue of the Journal Sharma et al report their experience of BP induced ONJ in two patients, the first being an elderly female having Rheumatoid Arthritis and receiving DMARDs along with low dose prednisolone and receiving BP for Osteoporotic Vertebral Fractures. The second case was a young female suffering from SLE and receiving varying doses of steroids. BP was prescribed for Osteoporosis prophylaxis. In both patients ONJ was triggered by dental treatment and responded well to discontinuation of BP, antibiotics and symptomatic therapy. The authors have not considered whether the co morbid conditions like RA or SLE would have contributed to the pathogenesis and prognosis of ONJ in their cases. Systemic conditions that may impede local vascular condition and increase the risk of ONJ include Glucocorticoid therapy, Diabetes, advance age, smoking and alcohol.

It is recently proposed that BP may have toxic effects on oral epithelium overlying areas of high bone BP concentrations, decreasing the ability of the oral mucosa to heal following local trauma such as tooth extraction. Data to support this hypothesis come from the case of contact stomatitis in a patient sucking BP tablets. Dental risk factors for ONJ include: 1. Clinically and radiographically evident periodontitis. Severe periodontitis with chronic infection and inflammation of the supporting alveolar bone is a major risk factor for ONJ. 2. Tooth extraction : upto 60% of cases of ONJ have been reported in patients having had a recent tooth extraction. 3. Concomitant or past oral infection. 4. Failed root canal treatment with retained periapical infection. 5. Trauma caused by removable dentures. 6. Implant placement, past or current : newly placed implants have a poor healing rate in patients receiving IV BP and hence are contraindicated. Previously placed implants may have a higher rate of failure. This warrents further study. The current report of Sharma et al brings out the need
for a registry to be maintained for all cases of BP associated ONJ. This will provide valuable information regarding the strength of association of risk factors of ONJ. For this a close collaboration among medical and dental experts will be needed and national societies like Indian Rheumatology Association and Indian Dental Association should take up this task of maintaining such a registry of patients of ONJ which will help in collecting prospective data for formulating recommendations for prevention and treatment of BP associated ONJ. Currently the published recommendations are based solely on expert opinion and anecdotal experience and not on evidence from prospective data.11

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