Assessing the utility of serum C-telopeptide cross-link of type 1 collagen as a predictor of bisphosphonate-related osteonecrosis of the jaw

A systematic review and meta-analysis

Reyes Enciso, PhD; Jill Keaton, DMD, MS; Nadia Saleh, BDS, MS; Azadeh Ahmadieh, DDS, MS; Glenn T. Clark, DDS, MS; Parish P. Sedghizadeh, DDS, MS

ABSTRACT

Background. The authors of this systematic review and meta-analysis assessed the utility of serum C-telopeptide cross-link of type 1 collagen (sCTX), a biomarker of bone resorption, as a predictor of the development of bisphosphonate-related osteonecrosis of the jaw (BRONJ).

Types of Studies Reviewed. The authors searched for studies involving adult participants, written in English, and published through January 20, 2016, using the following electronic databases: the Cochrane Library, MEDLINE via PubMed, and Web of Science. They also searched Google Scholar and the reference lists of all eligible trials and reviews. They identified 16 articles that met their inclusion criteria (9 controlled studies and 7 case series). They applied the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for systematic reviews and meta-analyses. They independently extracted data in duplicate, including the characteristics of study participants, risk factors, control groups, and outcomes. They assessed risk of bias, and they resolved any disagreements between review authors through discussion.

Results. A meta-analysis with 9 controlled studies revealed no significant difference in mean sCTX values between patients with BRONJ and control participants (difference in means, −31.417; 95% confidence interval [CI], −91.560 to 28.726; $P = .306$). A second meta-analysis with 4 studies showed no significant difference in risk of having an sCTX value below 150 picograms per milliliter for patients with BRONJ compared with control participants (risk ratio, 1.892; 95% CI, 0.636-5.626; $P = .251$).

Conclusions and Practical Implications. A systematic review of the literature with meta-analysis does not support the use of sCTX levels as a predictor of the development of BRONJ. Further prospective large sample studies are needed to understand the role of sCTX as a predictor for BRONJ.

Key Words. Bisphosphonate; BP; nitrogen-containing bisphosphonate; aminobisphosphonate; bisphosphonate-related osteonecrosis of the jaw; BRONJ; MRONJ; CTX.

JADA 2016:147(7):551-560

http://dx.doi.org/10.1016/j.adaj.2016.02.011

Bisphosphonate (BP) medications are used widely in the treatment of a variety of bone-related pathoses.[1,2] One serious adverse effect of these medications is bisphosphonate-related osteonecrosis of the jaw (BRONJ), a condition in which necrotic areas of infected bone develop in the jaw.[3] Although the exact incidence of BRONJ is unknown, reports suggest that there is a greater risk of development in patients with cancer being treated with intravenous (IV) administration of BPs than in patients with osteoporosis being treated with oral administration of BP.[4] In a multicenter, international, parallel group trial involving 3,340 patients with breast cancer receiving IV therapy with zoledronic acid, the investigators noted a 0.7% (95% confidence interval [CI], 0.3-1.1) occurrence of BRONJ.[5] The investigators of a survey study involving more than 13,000 Kaiser Permanente members receiving long-term orally administered BP therapy for osteoporosis noted a 0.10% (95% CI 0.05-0.20) occurrence of osteonecrosis of the jaw.[6] These investigators reported that the

Xtra Supplemental material is available online.

prevalence of BRONJ increases to 0.21% from a baseline of approximately 0% after having 4 years of exposure to orally administered BP.[6]

Other investigators have reported variable clinical presentations of BRONJ, with some patients being asymptomatic and others experiencing mobile teeth, soft-tissue inflammation, and altered neurosensory function.[7] Patients also can have exposed necrotic bone, pain, infection, and fistulas. Although there are no pathognomonic radiographic characteristics, investigators have reported radiographic findings associated with BRONJ, including thickening of the periodontal ligament, narrowing of the inferior alveolar canal, alveolar bone loss, persistent poorly healing alveolar bone sockets, and changes in trabecular pattern.[8] The American Association of Oral and Maxillofacial Surgeons (AAOMS) published a position paper in 2007,[8] with revisions published in 2009[9] and 2014,[4] to address the need for clarity. The AAOMS suggested the following criteria to establish the diagnosis of BRONJ: current or previous treatment with a BP, exposed necrotic bone in the maxillofacial region that has persisted for more than 8 weeks, and no history of radiation to the jaws. The 2014 AAOMS position paper update[4] recommended a change of the term BRONJ to medication-related osteonecrosis of the jaw (MRONJ) to reflect the growing number of osteonecrosis cases associated with non-BP antiresorptive drugs and antiangiogenic therapies.[4] Baim and Miller[10] commended the AAOMS for its efforts but asked for more clarity on the usefulness of serum C-telopeptide cross-link of type 1 collagen (sCTX) in BRONJ risk assessment.[11] In this study, we used the term BRONJ rather than MRONJ, as we focused specifically on BP-related cases and not those cases associated with other medications.

The assessment of risk of developing BRONJ after having an oral surgical procedure is a key clinical challenge. The condition, for which palliative treatment is a common approach, may persist for many years. Therefore, the application of a prevention strategy is a paramount goal, but it requires identifying patients at risk of developing the disease. Investigators have widely used levels of sCTX in this context.[9] During the bone-remodeling process, both bone formation and resorption occur.[10] During bone resorption, hydrochloric acid is secreted by osteoclasts, which dissolve bone minerals. The biochemical markers released during the bone-remodeling processes can provide a measure of the rate of bone metabolism. Investigators have used the sCTX marker primarily as a research tool to study the pathogenesis and treatment of bone disease.[10] In clinical practice, investigators have suggested the use of this biomarker to monitor the effectiveness of antiresorptive therapy, predict bone loss and fracture in patients with osteoporosis, and predict complications of metastatic bone disease and multiple myeloma; investigators also have used it in patients with rheumatoid arthritis to monitor the progression of joint damage.[12] Moreover, investigators have used sCTX levels as an indicator of increased bone resorption in menopausal women and as a follow-up tool in postmenopausal women.[10]

Clinicians have used BP drugs for decades for conditions in which alteration of bone metabolism is desired. Although the exact mechanism is unclear, it appears that BP drugs have both antiosteoclastic and antiangiogenic effects, altering the resorption and remodeling of bone.[13] In the presence of altered cell metabolism, patients experiencing trauma to the mandible or maxilla may experience an abnormal healing response, resulting in the exposure of necrotic bone to the oral cavity. For those patients receiving BP therapy for 3 years or more and for patients taking BP drugs along with corticosteroids for less than 3 years, investigators have recommended obtaining a morning fasting level of sCTX preoperatively.[14] There are many variables that affect sCTX measurement, including age, alcohol consumption, smoking, ovulation, sex, exercise, circadian rhythms, drugs such as corticosteroids, diseases such as diabetes, and laboratory testing variability.[15]

Some investigators have suggested that the level of sCTX may be used to assess osteoclast and osteoblast activity and thus predict which patients might develop BRONJ after having oral surgery. For example, Marx and colleagues[14] suggested the following regimen: if the patient has a fasting sCTX value of at least 150 picograms per milliliter, the clinician can schedule the patient for the planned surgical procedure because the patient has a minimal risk of developing BRONJ; if the patient's fasting sCTX value is equal to or less than 100 pg/mL, the clinician should consider the patient to have a high risk of developing BRONJ.

There is no consensus on how to best manage the dental treatment of a patient who is taking oral or receiving IV BP medication. Moreover, there is continuous debate on the utility of the sCTX test as a predictor of the development of BRONJ. Therefore, the objective of this systematic review and meta-analysis was to determine whether sCTX, a marker of bone resorption, could predict preoperatively the risk of developing BRONJ in patients taking BP.

METHODS

For our study, we limited the studies we selected to prospective and retrospective observational studies (case-control, cohort, or cross-sectional) and case series whose

ABBREVIATION KEY. **AAOMS:** American Association of Oral and Maxillofacial Surgeons. **BP:** Bisphosphonate. **BRONJ:** Bisphosphonate-related osteonecrosis of the jaw. **IV:** Intravenous. **MRONJ:** Medication-related osteonecrosis of the jaw. **sCTX:** Serum C-telopeptide cross-link of type 1 collagen.