Osteonecrosis of the Jaw and Biomarkers: What Do We Tell Our Patients?

Have you ever wondered why, when presented with a choice of therapies that have been fully discussed in terms of risks and benefits and consequences, patients still turn to their health-care provider and ask "What would you do if you were me?" According to Dr Victor Montori, a colleague at Mayo who studies decision making, patients ask this question for 1 or more of 3 reasons. First, it's possible that after all of the discussion, the patient is confused and realizes that he or she does not really understand the circumstances. Alternatively, the patient may have understood the discussion but believes that the health-care provider's experience and education trump his or her own understanding. Finally, the patient may have understood the discussion and is merely seeking confirmation of his or her own as-yet-unprofessed decision. I use this scenario-based commentary only to emphasize the importance of the role of the health-care provider as a principal gatekeeper of information and perspective. Patients routinely rely on us to provide them with information that represents evidence-driven best practice. Given that the scientific dental literature is growing rapidly and presents a daunting challenge to assimilate, this responsibility is potentially overwhelming. We are at the mercy of the peer-review process to provide an adequate level of scrutiny to meet appropriate scientific standards. However, despite the best of intentions, papers will occasionally be published that reach too far with their conclusions. If such a paper were to receive considerable attention without challenge, the consequences for clinical practice could be detrimental for patients and practitioners making decisions regarding therapy.

In my opinion, a recently published paper with the stated purpose of assessing the risk and time course of oral bisphosphonate-induced osteonecrosis of the jaws (ONJ) offers valuable insight into many aspects of this potentially devastating, but fortunately relatively uncommon, condition.[1] The authors have considerable experience managing patients with ONJ, and their desire to share their perspectives is laudable. However, one key part of the study focuses on measurements of serum levels of the protein C-terminal telopeptide (CTx), a degradation product of bone and a marker of bone resorption widely used as 1 of many surrogate markers of bone turnover. The authors obtained a serum CTx value prior to discontinuation of oral bisphosphonate therapy for a group of 17 patients presenting with ONJ (from a total of 30 described in the paper) and noted that the suppressed serum CTx levels increased once patients discontinued oral bisphosphonate therapy. Presented as nothing more than a confirmation of the effect of oral bisphosphonate therapy on serum CTx levels, such findings are entirely consistent with expectations. Nevertheless, the scientific method demands that claims of correlation should be made after statistical analysis of sufficiently large data sets obtained from validated objective outcome measures. Yet in spite of a small study population and lack of data relating serum CTx levels to any defined and validated objective measures of ONJ severity at presentation or of healing response, the authors state that the improvement in serum CTx levels "correlated to either spontaneous resolution of the exposed bone, a significant improvement in the amount of exposed bone, or an uncomplicated healing response after surgery." Despite a lack of objective measures to support their subjective assessments, the authors make clinical treatment recommendations that interpret serum CTx levels "of less than 100 pg/mL as high risk, 100 pg/mL to 150 pg/mL as moderate risk, and greater than 150 pg/mL as minimal risk" and state that "the morning fasting serum C-terminal telopeptide bone suppression marker is a useful tool for the clinician to assess risks and guide treatment decisions." These statements drastically overextend findings resulting from a subjective assessment of 17 subjects to create clinical practice recommendations that are sweeping in nature even though the authors' interpretation of the clinical outcomes may have merit. The authors failed to reconcile their statements with the fact that there are likely to be thousands of patients with serum CTx values of less than 100 pg/mL who have not experienced healing problems after dental surgery. Regrettably, patients on oral bisphosphonates who healed well after dental extractions were not included in the serum CTx assessment. Hence, the lack of a control comparison cohort undermines the validity of the authors' conclusions.

In my opinion, there is a potential flaw in the logic that connects the 3 dots represented by *(1)* the association of oral bisphosphonate therapy with ONJ; *(2)*

the expected effect of oral bisphosphonate therapy on serum CTx levels; and *(3)* the expected effect of discontinuation of oral bisphosphonate therapy on serum CTx levels, with a fourth dot of the authors' subjective determination that some patients who discontinued therapy responded well. In addition, it is unclear how valuable a systemic bone marker ultimately will prove to be relative to ONJ given the comparative rarity of osteonecrosis observed at non-oral sites in patients receiving intravenous or oral bisphosphonates. If an objective assessment of a sufficient number of subjects to allow meaningful statistical analysis demonstrates correlation between serum CTx levels and ONJ-related responses, then one should accept that such an association does exist. For now, however, the burden of proof has not been met.

So what is the unsuspecting dedicated clinical practitioner to do? To make use of evidence-based practice concepts to help patients make decisions about their therapy is particularly challenging when the body of evidence on a given topic, such as ONJ, is relatively small. This paper proposing a link between ONJ and CTx levels reminds me of similarly flawed logic used to create some humorous graffiti I had occasion to read a few years back:

God is love
Love is blind
Ray Charles is blind
Therefore, Ray Charles is God

The high hopes that we all entertain at the sight of a new paper containing recommendations for clinical practice in any field must be tempered with insistence that the burden of proof for these recommendations be founded on the rigorous application of the scientific method and proper scrutiny of the peer-review process. Anything less undermines our best efforts to care for our patients and leaves our profession vulnerable to the charge of being blind to our responsibility to society.

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1. Marx RE, Cillo JE Jr , Ulloa JJ. Oral bisphosphonate-induced osteonecrosis: Risk factors, prediction of risk using serum CTx testing, prevention and treatment. J Oral Maxillofac Surg 2007;65:2397–2410.