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Current Opinion on MRONJ

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Introductory Review

Patients on antiresorptive medication have been increasing since the introduction of the bisphosphonates as an effective agent. As an antiresorptive agent bisphosphonate has substantial effect in treatment of osteoporosis, and its antiangiogenic potential renders it a powerful anticancer effect. With all the fantastic effect, it has a critical result of jaw bone necrosis, namely bisphosphonate-related osteonecrosis of the jaw (BRONJ). Although extremely rare [1,2], the number of cases reporting this phenomenon is growing worldwide [3-8]. The special committee dealing with the problem of osteonecrosis found on the jaw bones of patients on bisphosphonate recommends changing the nomenclature BRONJ for medication-related osteonecrosis of the jaw (MRONJ) [9]. It is based on the new findings of jaw bone necrosis related to other types of antiresorptive drugs including Denosumab (Prolia®), a monoclonal antibody to RANK ligand, and other antiangiogenic agents such as Becacizumab (Avastin®). Established as a clinically significant disease entity, investigation of MRONJ needs further considerations into the risk factors and drug holiday as a means of prognostic improvement.

Systemic Risk Factors

There are many studies revealing that age of the patients, potency of the bisphosphonates, coexistence of other medical diseases and dental extraction are major risk factors of MRONJ [7,10-13]. Excluding patient's age which is a fixed factor, other risk factors must be evaluated for improvement of MRONJ. Generally, nitrogen containing bisphosphonates are more potent than non-nitrogen containing ones [14]. Non-nitrogen containing bisphosphonate is supposed to be involved in pyrophosphate metabolism which creates biochemically refractory ATP analogues. Nitrogen-containing bisphosphonate is known to show its pharmacological activity via mevalonate pathway. The difference of action mechanism between these two bisphosphonates may have something to do with the potency difference [15].

While low dose PO bisphosphonates are prescribed for antiosteoporotic effect, high dose bisphosphonates are administered via intravenous route in cancer patients. According to AAOMS position paper on MRONJ 2014 update [9], the highest estimate for MRONJ risk in patients on antioesteoporotic PO bisphosphonate was 0.1% [16]. And in a meta-analysis of the incidence of MRONJ after dental extraction, the overall occurrences was 3.2% in IV antiresorptives for cancer patients and 0.15% in PO bisphosphonates for osteoporosis, respectively [12]. It was revealed that high IV dose of bisphosphonates are more prone to cause MRONJ.

Significant risk factors are known to be the duration of therapy and existence of comorbidity factors [9]. The duration of drug administration is one of the criteria in grouping the MRONJ patients. Patients on antiosteoporotic agent for more than 4 years are categorized into high risk group. Patients on antiosteoporotic agent for less than 4 years are categorized into low risk group unless they have comorbidities such as diabetes or steroid injection. Briefly, patients who are on antiresorptive or antiangiogenic medication considered high risk group, if they are either on antiosteoporotic treatment for more than 4 years or with medical comorbidities.

Dental Risk Factors

The importance of tooth extraction as a local risk factor for MRONJ is ever increasing now-a-days [8,12]. Early detection of the MRONJ has usually been by dentists because they are acquainted with patients' oral findings. With increasing importance of dental extraction as a risk factor for MRONJ, dentists' role as an early finder for MRONJ becomes more evident.

Development of MRONJ after extraction is not a technical problem but an undefined pathological problem. Currently most probable hypothesis is the osteoclastic dysfunction [9,17]. Others suggest infection may play a role in its pathogenesis [18] or immunologic dysfunction may be the causative factor [19,20]. Having an ambigue pathophysiology, empirical evidence is more practical for now. Recent update of AAOMS position paper [9] estimated the 0.5% incidence of MRONJ after dental extraction of patients on antiosteoporotic PO bisphosphonates on the basis of a single study [21]. A study of surgical tooth extraction underwent in 61 high-risk patients concluded no statistically significant differences between BRONJ (MRONJ)-developed group and healthy group except the parameter of "the need for additional osteotomy" [22]. It is therefore important that a traumatic surgery is a kind of preventive measures in surgical tooth extraction in high-risk patients. Waiting for further data accumulation, my current opinion as an expert is that all bone-involving surgery should be considered a risk factor, because all surgical traumas involving bone remodeling must be categorized into the same risk factor as a dental extraction.

Drug Holiday

Recent AAOMS position paper recommends established osteonecrosis as the guidance to consider discontinuing bisphosphonates in antiresorptive therapy for osteoporosis or cancer [9]. The paucity of data upon drug holiday in the position paper allows the absence of the definite declaration of drug holiday in asymptomatic patients receiving antiosteoporotic medications with high risk groups. Recent data however shows drug holiday reduces MRONJ incidence and severity [23], which justifies clear statement of drug holiday. It is desired that clear declaration of the drug holiday for the patients on all kind of the antiresorptive and antiangiogenic medication is stated in the future position paper.

Argument on adequate duration of drug holiday is still ongoing. Pharmacokinetic approach to calculate optimal drug holiday yielded 2 months of duration on the basis of the serum bisphosphonate level [24]. Although still obscure, current opinion on the pathophysiology of MRONJ insinuates that osteoclastic dysfunction by absorbed bisphosphonate, not serum bisphosphonate is the etiologic factor for MRONJ, which undermines just above suggestion. On the other hand, a clinical study on MRONJ suggests 4 months of drug holiday [25]. Being a retrospective study not randomized, it is also based on low level evidence. Neither of these data is based on high level evidences, which requires more data to draw accurate conclusion on drug holiday. Considering these, recent Korean Position Paper recommends at least 2-4 months of drug holiday on high risk patients receiving antiosteoporotic medications [26]. On the contrary, drug holiday for Denosumab is more lucid because MRONJ related to Denosumab may resolve in 6 months according to the effective duration of this medication [27]. While there are other means to seek prognosis evaluation [28], such efforts to establish optimal drug holiday is expected to be the milestone for improving surgical prognosis of MRONJ.

Concluding Remarks

Although uncommon, seriously threatening the quality of life, MRONJ is a clearly defined disease entity in oral and maxillofacial surgery. Still obscure in defining pathophysiology, in selecting treatment method, and in estimating prognosis of this disease, future endeavor should be focused upon improving quality of patients' life. Determining risk factors, seeking optimal treatment method, and maximizing prognosis improvement will serve this purpose.

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