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Review

Treatment perspectives for medication-related osteonecrosis of the jaw (MRONJ)

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ABSTRACT

The medication-related osteonecrosis of the jaw (MRONJ) is believed to be a therapy-resistant entity. Although the application of the recommended conservative and surgical treatment regimens have returned variable success rates, the increased awareness and experience with MRONJ suggests that surgical therapy can halt the progression of the disease, thereby allowing a histology-based diagnosis of the osteonecrosis. Surgical treatment protocols can achieve success rates of over 90% and novel techniques such as the visualization of bone fluorescence can assist in the intra-operative delineation of the osteonecrosis and standardize the procedure.

1. Comment on the status quo

The community of oral and maxillofacial surgeons has yet to agree on a universally acceptable therapy strategy of the medication-related osteonecrosis of the jaw (MRONJ), in particular for the bisphosphonate related osteonecrosis of the jaw (BRONJ) as well as the denosumab related osteonecrosis of the jaw (DRONJ).

In a recent position paper, the American Association of Oral and Maxillofacial Surgery (AAOMS) published stage specific treatment recommendations for MRONJ (Ruggiero et al., 2014). In essence, the AAOMS recommendations echoed those stated in 2007 and 2009 for BRONJ (2007), namely supporting conservative therapy, with aggressive surgery offered only to symptomatic patients. In contrast, the MRONJ guideline report from the German Dental and the German Oral and Maxillofacial Associations refrains from recommending therapy recommendations at least for certain stages of the disease (Groetz et al., 2012).

The reason might be several-fold and linked to the pitfalls of the current MRONJ staging criteria (Ruggiero et al., 2009): (i) neither the extent of the exposed bone nor its localization is taken into account, (ii) multi-factorial MRONJ symptoms are not evaluated and are therefore disregarded, (iii) the general condition as well as the patients' burden of suffering are commonly not respected, (iv) disease quality (bone metastasis or osteoporosis) as well as prognosis affecting co-morbidities are, at large, ignored, and (v) the extend of the osteonecrosis is frequently not correctly identified, possibly influencing the therapeutic strategies (Bedogni et al., 2014).

Despite the (re)new(ed) AAOMS recommendations, success rates of conservative treatment regimens range from less than 20% (Marx et al., 2005; Hoff et al., 2008; Montebugnoli et al., 2007; O'Ryan et al., 2009; Watters et al., 2013) to above 50 % (Badros et al., 2008; Van den Wyngaert et al., 2009) which is significantly lower than the therapy success of over 85% reported for surgical approaches (Pautke et al., 2011; Stockmann et al., 2010; Voss et al., 2012; Carlson and Basile, 2009). The qualitative definition of therapy success may be a contributing factor of the observed

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discrepancy in the success rate of conservative treatments. By minimizing symptoms and infections (Badros et al., 2008; Van den Wyngaert et al., 2009) an intermittent improvement may be achieved but should not be classed as therapy success the disease or the elimination of the osteonecrosis. This notion might explain why many investigators (correctly) conclude that MRONJ is a relapsing and remitting diagnosis. Indeed, Carlson postulated that the conservative management typically relates to the palliation of osteonecrosis, whereas surgical resection most commonly translates in a cure of the patient's disease (Carlson, 2014). It is advisable that the success of a therapy is assessed via prospective (rather than retrospective) study designs. A retrospective study conducted with questionnaires and without oral investigations will not be sufficiently powerful to detect the early or 'silent' stages of MRONJ (stage 0 and 1), characterized by complaints in the jaw bone region without exposed bone or by exposed bone not accompanied by infection or pain, respectively. Indeed, any superficial clinical staging of bony disease may result in the under- or over-estimation of the disease, thereby resulting in misinterpretations and repercussion on therapeutic decisions. A recently published MISSION study (Bedogni et al., 2014) reported that the AAOMS system misclassified/underestimated the severity of the disease at a rate of about 1 in 3, in particular in patients suffering from MRONJ stage 1 and 2. The authors conclude that these findings may explain why the treatment of stage 3 osteonecrosis, namely surgery, has been deemed to be more predictable and therefore yields more favorable outcomes than the treatment of AAOMS stages 1 and 2 (Graziani et al., 2012).

MRONJ is currently diagnosed if exposed jawbone is exposed for a period that exceeds 8 weeks (AAOMS, 2007; Khan et al., 2014; Khosla et al., 2007; Ruggiero et al., 2009), a positive history for the respective antiresorptive drug and no irradiation of the jaw regions. Therapy involves the removal of the exposed necrotic bone to allow the restoration of the mucosal integrity (Carlson and Basile, 2009). Given that necrotic and exposed bone will not revitalize, resurrected MRONJ should be removed, in particular in light of the fact that small residuals can lead to a recurrence or progression of MRONJ due to mechanical injury of the mucosa. In addition, exposed bone is susceptible to bacterial colonization and infection, in particular the gram-positive actinomyces (Schipmann et al., 2013; Sedghizadeh et al., 2008). Microbes may therefore play a role in the pathogenesis and aggravation of an existing MRONJ. Conservative treatment approaches commonly do not result in a mucosal healing over the area of exposed bone (Marx et al., 2005; Montebugnoli et al., 2007), thereby increasing the risk of secondary infections that may lead to abscesses or pain, particularly in immuno-compromised patients. An additional burden of conservative therapy is the weekly or twice-weekly wound management consultations typically spanning a time period of several months to years (O'Ryan et al., 2009; Hoff et al., 2008). What should not be discounted is the habituation effect of the microbial wound flora (microbial resistances or oral candidiasis) following extended periods of antibiotic treatment (Hoefert and Eufinger, 2011). Timely treatment therefore has a positive effect on the diseases outcome (Ruggiero et al., 2004; Otto et al., 2009) and surgical treatment is notably completed usually within 3–4 weeks (Pautke et al., 2011). One may argue, and this is in line with others (Carlson, 2014), that it is unlikely that osteonecrosis will heal without recurrence by the sole removal of bone sequesters without the treatment of the underlying osteonecrosis.

The surgical approach also allows the harvesting of tissue to aid in the diagnosis of osteonecrosis by means of histopathological investigations. Although until now the histopathological proof of an osteonecrosis is not a part of its definition, it can exclude the presence of other pathologic conditions such as jawbone metastasis (Otto et al., 2010b) which require bespoke treatments. Therefore, this perspective aims to reinforce the view that MRONJ therapy should focus on resolving the leading symptom, namely the exposed bone. The authors firmly believe that further advances in the MRONJ therapy will be achieved if surgical therapy is considered even for early MRONJ stages. Further investigations will be necessary to highlight this assertion.

However, conservative therapy can be useful, in fact may be necessary, when a patient's general condition does not allow surgical intervention or further chemotherapy is required. The application of conservative measures can improve or stay asymptomatic in up to 70% of the cases (Lerman et al., 2013), notably, this cannot considered as therapy success but as temporary relief. In any case it is crucial that patients are informed about different treatment options, the duration, burden and discomforts of each therapy, as well as the predicted success rates.

2. Surgical appeal

It is generally accepted that surgical therapy is required when chronic necrotic tissue is encountered, since dead tissue cannot be resurrected and interfere with wound healing (Carlson, 2014; Carlson and Basile, 2009). Common sense dictates that it is best to resect as much as necessary but as little as possible. Therefore two surgical approaches have emerged, namely (i) debridement and (ii) resection (Graziani et al., 2012) which are characterized by different success rates (Carlson, 2014; Graziani et al., 2012; Jabbour et al., 2012).

Debridement makes use of a cautious and empirical application of bone curetting to reduce but not completely eliminate necrotic bone (Carlson and Basile, 2009; Graziani et al., 2012). In contrast, resection applies a calculated removal of necrotic bone with a subsequent normal bone margin based on preoperative imaging performed as marginal, segmental or even subtotal to total resection.

The challenge and limitation of both surgical techniques is the determination of the precise margins of the osteonecrosis, i.e. a clear demarcation of the necrotic bone is difficult, if not impossible (AAOMS, 2007; Khan et al., 2014; Khosla et al., 2007; Pautke et al., 2009). Whilst the complete removal of necrotic bone is of crucial importance (Mücke et al., 2011; Carlson and Basile, 2009), an unintentional or excessive removal of healthy bone must be avoided to ensure the jawbone is not weakened and to maximize the chances for a dental or prosthetic rehabilitation. Both surgical techniques (debridement and resection) cannot be standardized due to the lack of guidance that defines the margins of the necrosis. Therefore, surgical therapy is at large dependent on the experience of the surgeon and comparisons between surgical units are therefore, by definition, difficult. Numerous imaging aids are able to visualize the extent of the osteonecrosis (Hutchinson et al., 2010; Fabbricini et al., 2009; Dore et al., 2009; Guggenberger et al., 2013). Although certain radiologic diagnostic devices are suitable modalities that are able to identify bone necrosis (Bedogni et al., 2014), a reliable technique capable of fully defining the extent of the necrosis preoperatively is still elusive (Groetz et al., 2012).

Arguably the most reliable parameter is the intraoperative impression of the surgeon (Guggenberger et al., 2013). The MRONJ therapy entails the surgical debridement until the bone appears to be "normal" in terms of bone structure, color and texture. The exposed bone in MRONJ lesions is typically darker and yellowish in color (compared to the unaffected sites). Due to the increased porosity, necrotic bone is often softer and surrounded by sclerotic areas, which in turn is harder and less vascularized. Bone bleeding is considered to indicate viable bone in the surgical therapy of osteonecrosis and in particular MRONJ. However, bone bleeding