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Original Article

# Clinical analysis of medication related osteonecrosis of the jaws: A growing severe complication in China

Qizhang Wang<sup>a,1</sup>, Jiyuan Liu<sup>a,1</sup>, Shuqun Qi<sup>a,1</sup>, Xuejuan Liao<sup>a,1</sup>,  
Dazhong Liu<sup>b,1</sup>, Jian Pan<sup>a\*,1</sup>

<sup>a</sup> State Key Laboratory of Oral Diseases, National Clinical Research Center for Oral Diseases, Dept. of Oral and Maxillofacial Surgery, West China Hospital of Stomatology, Sichuan University, Chengdu, Sichuan Province, China

<sup>b</sup> Xindu District Peoples Hospital of Chengdu, Sichuan Province, China

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## KEYWORDS

Bisphosphate;  
Osteonecrosis;  
Risk factor;  
Treatment

**Abstract** *Background/purpose:* Medication-related osteonecrosis of the jaws (MRONJ) is an unusual but quite serious complication. However, its mechanism remains unclear, and its treatment protocol is still controversial.

*Materials and methods:* Our study involved 201 osteonecrosis of the jaw (ONJ) patients from September 2006 to March 2017. We analyzed risk factors, clinical characteristics, treatment, etc., by comparing MRONJ with other ONJs.

*Results:* Among 201 patients, MRONJ accounted for 14.71% and it presented a consistent increase tendency. In comparison with other ONJs, we considered advanced age, maxilla lesion, diabetes mellitus, tooth extraction, especially multi-teeth extraction as risk factors ( $P < 0.0125$ ). Our study demonstrated that maxillary lesion was associated with an advanced stage and it was inclined to worse prognoses. We also found MRONJ had little correlation to Actinomyces infection. Surgical treatment could improve patients' condition successfully ( $P > 0.05$ ). 81.3% patients with advanced stage showed complete or partial healing lesions after surgery.

*Conclusion:* Advanced age, maxilla lesion, diabetes mellitus, tooth extraction seem to be important triggering factors for MRONJ. Clinicians and surgeons should pay attention to maxillary lesions as it is related to severe symptoms and unfavorable prognosis. Once diagnosed as MRONJ, surgery is an effective treatment for patients with advanced stage.

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\* Corresponding author. Department of Oral and Maxillofacial Surgery, West China Hospital of Stomatology, Sichuan University, No. 14, Section 3rd, Renmin Nan Road. Chengdu, Sichuan, 610041, China.

E-mail address: [jianpancn@163.com](mailto:jianpancn@163.com) (J. Pan).

<sup>1</sup> These authors contributed equally to this work and should be considered co-first authors.

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## Introduction

Osteonecrosis of the jaw (ONJ) is a common oral and maxillofacial surgery disease. Since 2003, a new sort of ONJ, Bisphosphonate related osteonecrosis of the jaws (BRONJ), has been observed through ever increasing case reports.<sup>1</sup> Briefly, BRONJ is an unusual but quite serious complication of bisphosphonate (BP) therapy in patients suffering from osteoporosis or malignancies, such as multiple myeloma, breast cancer, prostate cancer, etc. In 2014 AAOMS' position paper,<sup>2</sup> BRONJ was replaced by MRONJ (Medication-related osteonecrosis of the jaws), as new drugs, for example, denosumab,<sup>3,4</sup> bevacizumab can also lead to osteonecrosis of the jaws. Though the incidence of MRONJ remains relatively low (0.7–6.7% for IV BPs, 0.1–0.21% for oral BPs),<sup>2</sup> it is lack of effective treatment protocol. Neither surgery nor conservative therapy can thoroughly eliminate patients' symptoms and reach complete healed oral mucosa. In addition, the pathogenesis of MRONJ is unclear even though a great number of researchers have been working on it. Possible hypotheses include inhibition of bone remodeling, anti-angiogenesis effect, bacterial infection, immunity dysfunction and direct cytotoxicity.<sup>5</sup> In China, a growing number of patients with osteoporosis, malignancies or bone cancer metastasis get in touch with BPs. Consequently, the incidence of MRONJ keeps rising. Though it can be easily diagnosed following the guidance of AAOMS,<sup>2,6</sup> difficulty lies in the treatment of MRONJ. The aim of our study is to compare MRONJ with other ONJs in West China Hospital from growing tendency, risk factors, clinical characteristics, treatment and outcomes, and so on, in order to propose guidelines customized for China population.

## Materials and methods

The database of the West China Hospital of Stomatology was searched from September 2006 to March 2017. Patients who visited the West China Hospital of Stomatology and diagnosed with either osteonecrosis of the jaw or osteomyelitis of the jaws were included. The inclusion criteria of MRONJ is according to AAOMS' definition,<sup>2</sup> and the main exclusion criteria of MRONJ were osteonecrosis after radiotherapy in head and neck area and obvious metastatic infiltration of the jaw. Patients who developed into osteonecrosis after bone graft were also excluded. *This study has*

*been approved by the Regional Ethics Committee Investigation of West China Hospital of Stomatology (WCHSIRB-D-2017-060). 201 patients were eventually selected into the study. Considering the classification of previous study<sup>7</sup> as well as the cause of osteonecrosis, patients were classified as five groups in our study:*

1. Medication related osteonecrosis of the jaws (MRONJ) group: patients have a previous or ongoing bisphosphonate treatment history but no head and neck radiation history. Our study didn't find any patients using denosumab or other drugs.
2. Osteoradionecrosis (ORN): Patients went through head and neck radiotherapy before osteonecrosis occurred on the mandible or maxilla.
3. Odontogenic osteonecrosis: Patients with dental infections, such as pericoronitis, developed into osteonecrosis or osteomyelitis with sequestra.
4. Trauma and surgical induced osteonecrosis: Patients were previously exposed to oral or maxillofacial trauma, leading to osteonecrosis or osteomyelitis with sequestra. Or patients went through oral and maxillofacial surgery, subsequently suffered from postoperative infection.
5. Cause-Unknown: Patients with no clear cause.

In the current study, in most cases, we compared the MRONJ group with other groups to figure out specific MRONJ risk factors and other useful statistics.

## Statistical analysis

SPSS (version 21.0, SPSS Inc., Chicago, IL, USA) was used to analyze the collected data. We analyzed descriptive statistics, and results were expressed in mean, standard deviation, frequency, percentage for different variables.

The Anova was applied for the study of the association of qualitative variables. To detect any differences between qualitative variables, the Pearson Chi Square test or Fisher's exact test, Bonferroni correction, Mann–Whitney U test were used as appropriate.  $P \leq 0.05$  were considered statistically significant.

## Results

201 patients were selected into our study. According to the statistics, odontogenic osteonecrosis was the most frequent

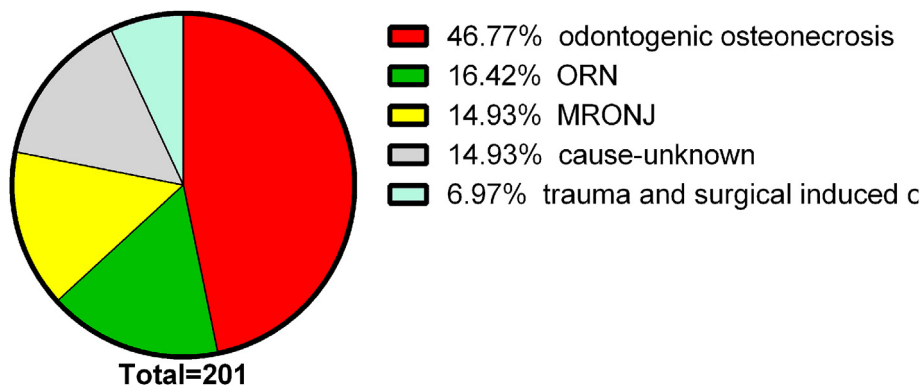


Figure 1 The fraction of each osteonecrosis.

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