

Necessity of drug holidays for patients treated with bisphosphonates in ARONJ prevention

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Objectives

Recently, it has been controversial whether taking drug holidays of bisphosphonates before tooth extraction is effective or not to prevent the onset of anti-resorptive agents-related osteonecrosis of jaws (ARONJ). For the management of patients receiving oral bisphosphonates (BP), the position paper was reported by the Allied Task Force Committee of the Japanese Society for Bone and Mineral Research in 2016. Since it is unclear that the relationship between taking drug holidays and the onset of ARONJ, we cannot strongly recommend patients take drug holidays before tooth extraction. The aim of this study was to examine the relationship between the taking drug holidays of BP and the onset of ARONJ.

Fig. 1. The rate of BP drug holiday in our department was getting decreased

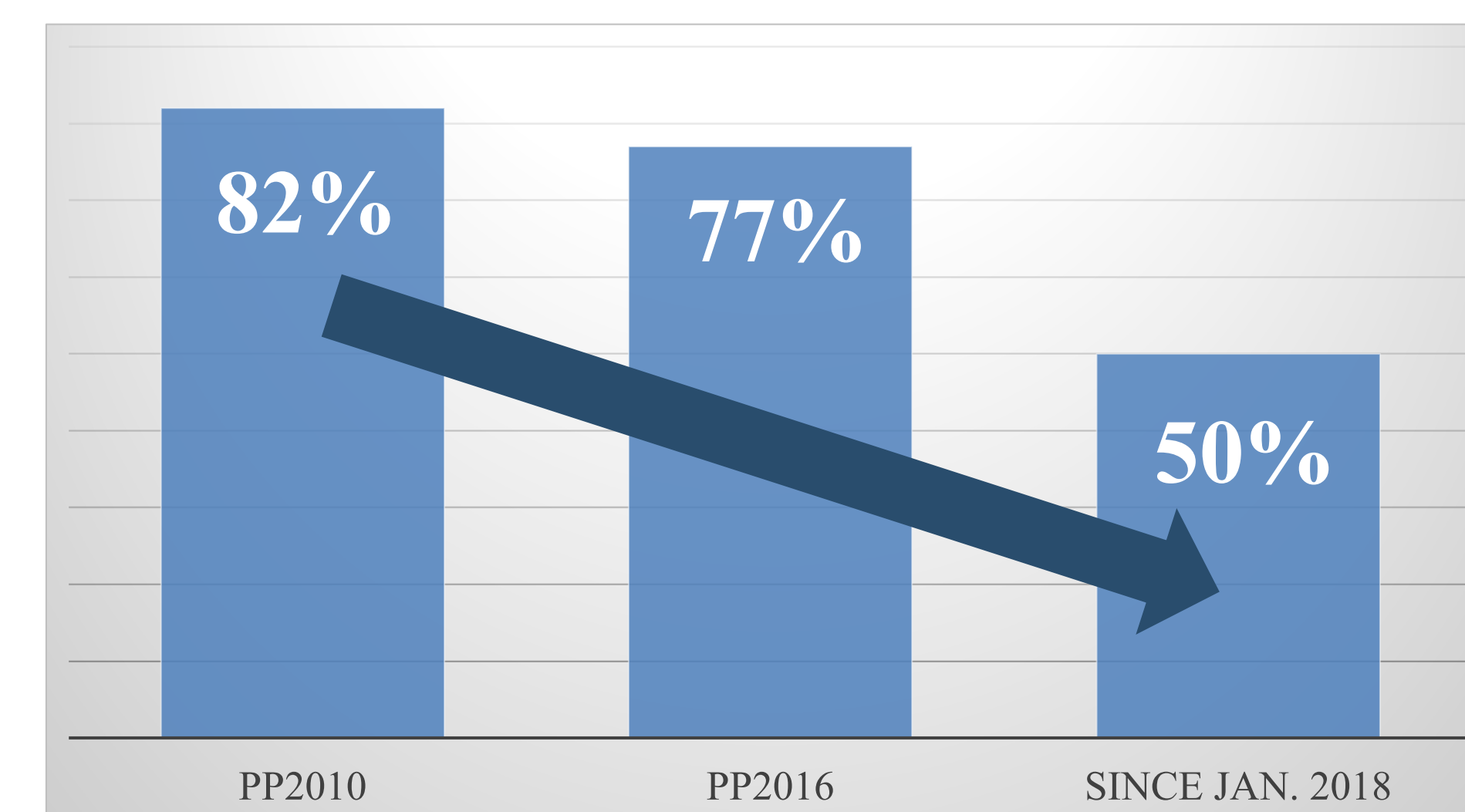
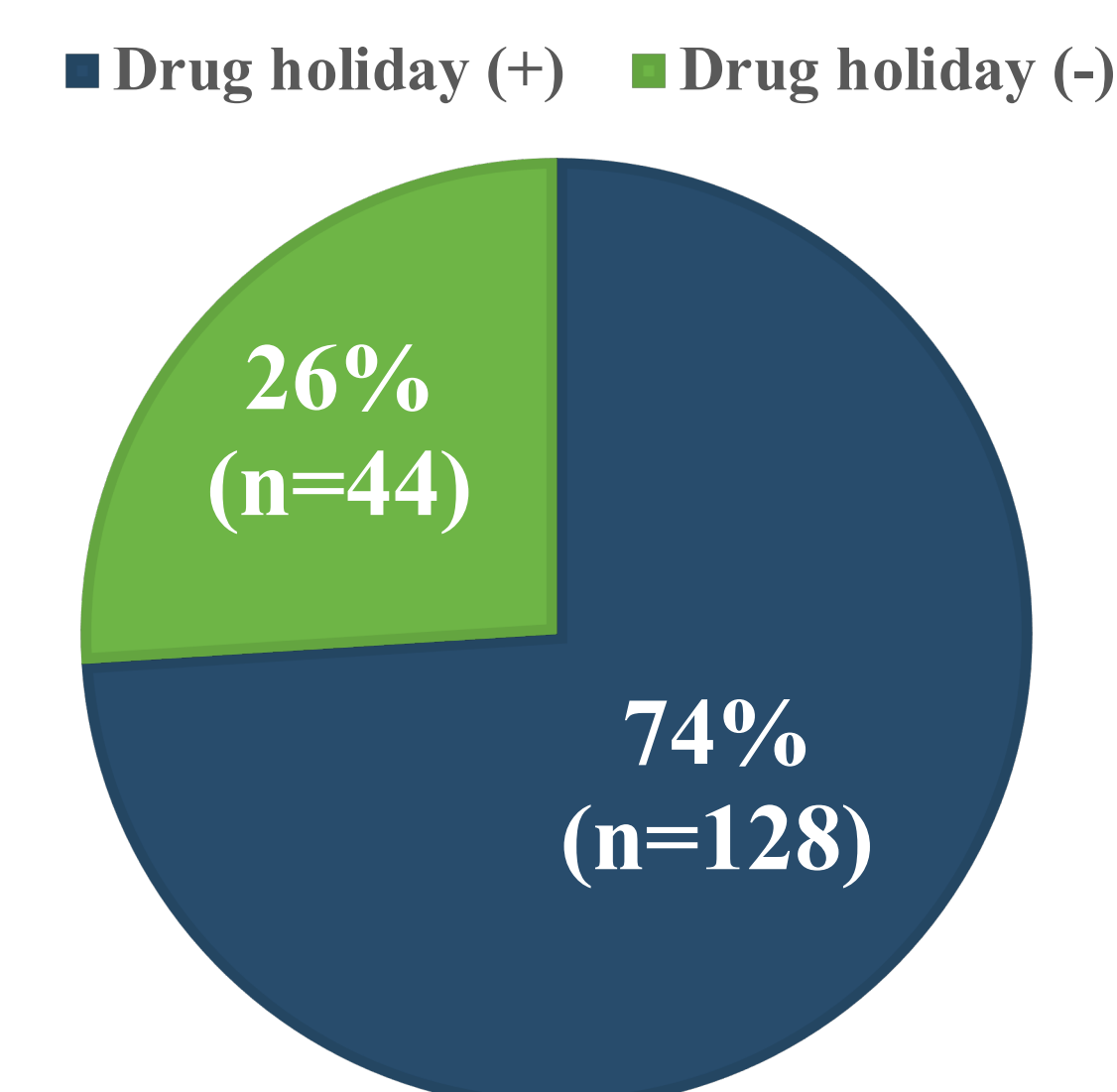
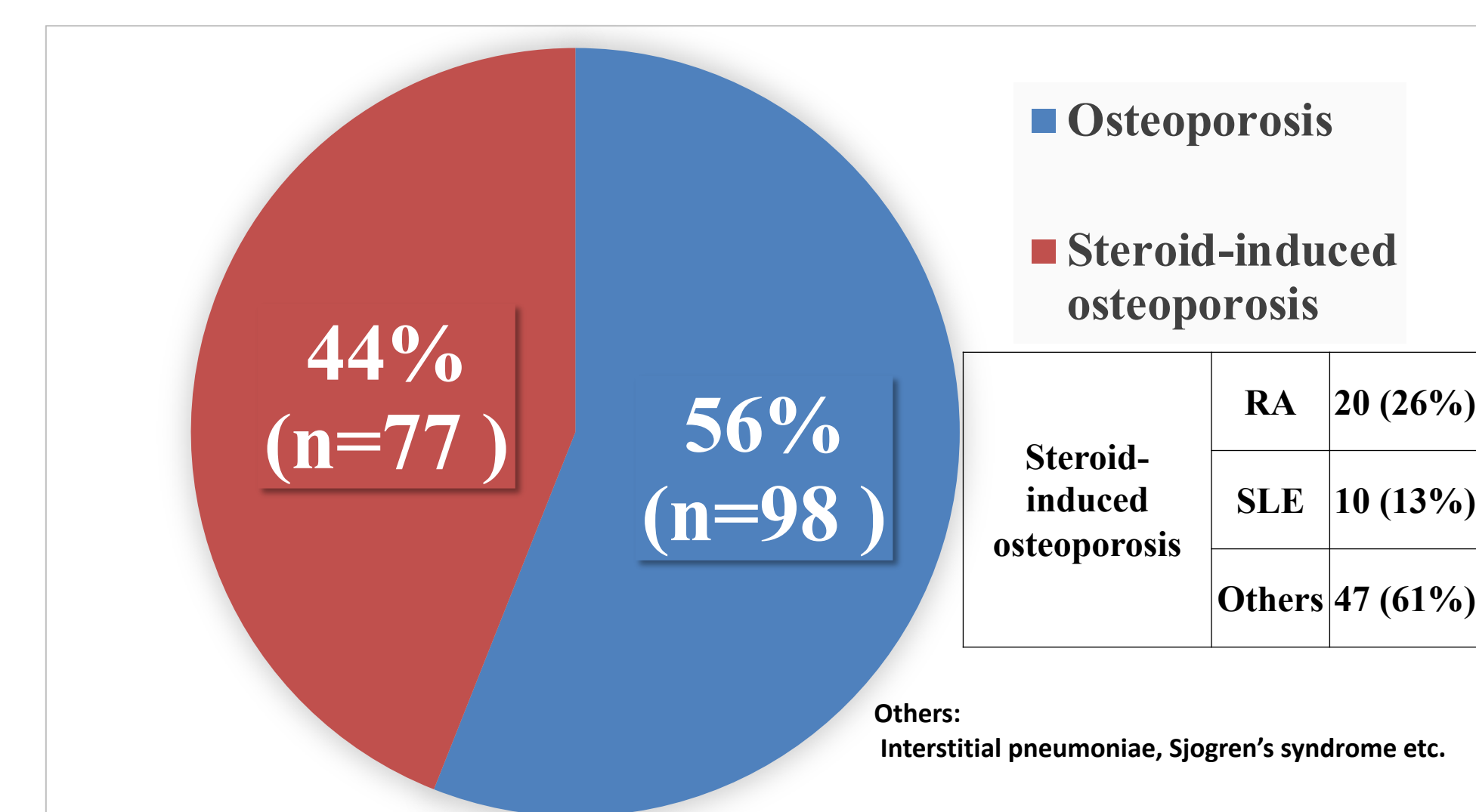


Fig. 2. Primary diseases in 172 patients



Methods

Between February 2012 and August 2018, 172 patients (Female: 147 cases, median age: 74 years old (25-99)) with a history of being treated by oral bisphosphonates underwent tooth extraction in our department.

We excluded patients with a history of taking intravenous bisphosphonates and denosumab.

We performed a multiple logistic regression analysis to investigate the relationships between the onset of ARONJ and its risk factors including sex, age, primary disease, the sites and types of tooth extraction, primary wound closure, and drug holiday.

Our study was approved by the Independent Ethics Committee of Hokkaido university Graduate School of Medicine (No. 018-0399).

Fig. 3. Outcomes of 172 patients

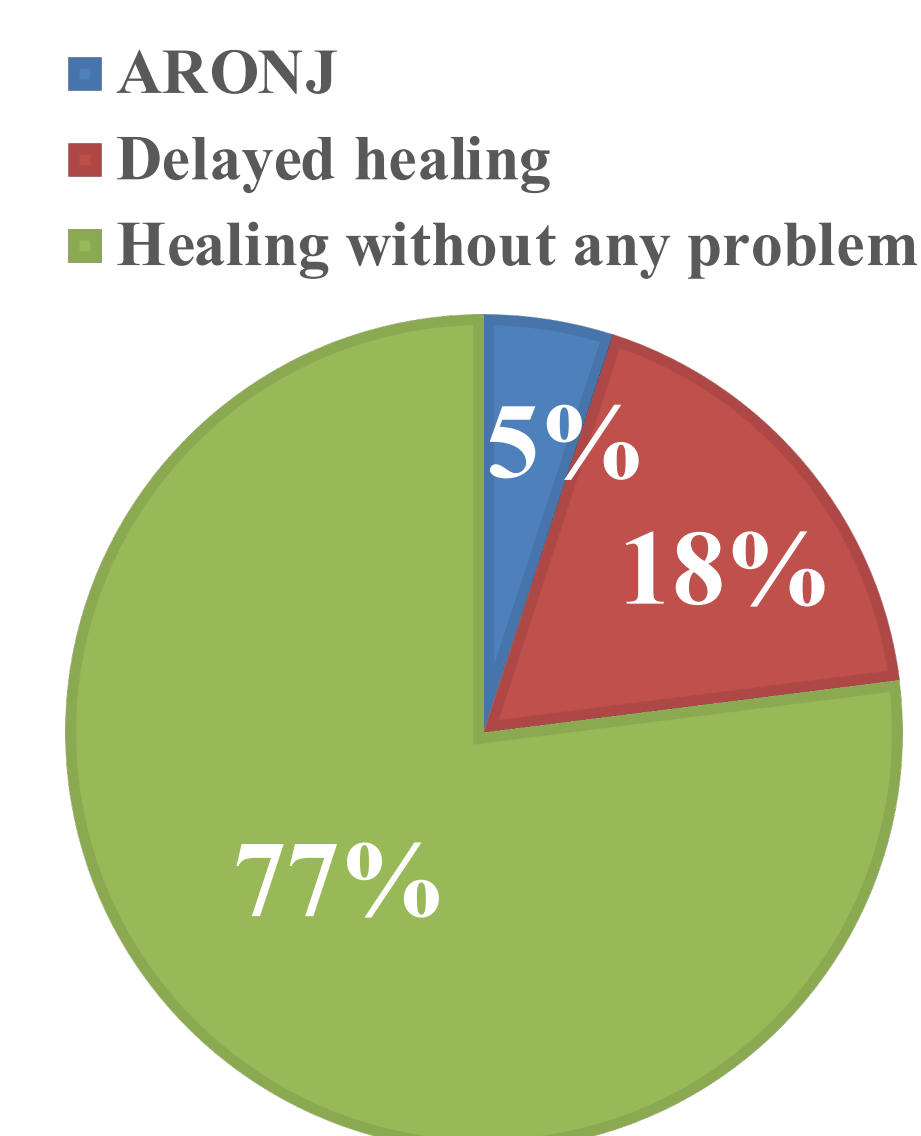


Fig. 4. ARONJ risk factors and the development of ARONJ

ARONJ risk factors	ARONJ (+)		ARONJ (-)	
	n=9	n=163	n=9	n=163
Sex	male (n=25)	2	23	
	female (n=147)	7	140	
Age	Median (yr)	76 (42-87)	74 (32-99)	
	Osteoporosis	5	93	
Primary disease	Steroid-induced osteoporosis	4	70	
	1st generation	0	83	
BP	2nd/3rd generation	9	80	
	Duration of BPs	Median (mo)	60 (4-120)	36 (1-150)
Drug holidays	Yes	8	120	
	No	1	43	
Tooth extraction site	including mandibular	5	103	
	Maxilar only	4	60	
Tooth extraction type	including molars and premolars	8	135	
	incisors only	1	28	
Wound closure	Yes	8	133	
	No	1	30	

Results

● Rate of drug holiday

Drug holidays was performed in 128 patients (74%), and the rate was declining (50%) in 2018 (Fig.1).

● Primary diseases

Of 172 patients, 98 patients (56%) were affected with osteoporosis and 77 patients (44%) were with steroid-induced osteoporosis (3 patients were overlapped). Rheumatoid arthritis was the most frequent in a steroid-induced osteoporosis group (26%), followed by Systemic Lupus Erythematosus (13%) (Fig.2). Median duration of BPs in a group of osteoporosis vs. of steroid-induced osteoporosis was 36 months vs. 33 months, respectively. We experienced a patient with compression fracture.

● Development of ARONJ and delayed healing

Of 172 patients, nine patients (5.0%) developed ARONJ (stage 0: one patient and stage 1: eight patients) and 31 patients (18%) developed delayed healing* (Fig.3).

Of nine patients with ARONJ, seven patients were female, five patients were affected with osteoporosis, and every patient underwent tooth extraction due to periapical periodontitis.

Five patients developed ARONJ at the mandibular, and every patient received 2nd and/or 3rd generation containing nitrogen BP. Median duration of receiving BPs was 60 months (10-120 months), and eight patients underwent drug holidays before tooth extraction (Fig.4).

Every ARONJ patient had bony exposure limited in alveolar bone and could be well-controlled by minimally invasive surgical procedure (Table 1).

● Statistical analysis

A multiple logistic regression analysis showed no significant difference between the two groups in the prevention of ARONJ in terms of drug holidays ($P = 0.38$). Development of ARONJ and patients' age was related to **positive correlation**. (Fig.5)

Delayed healing*: defined as taking more than one month and less than two months to achieve socket healing.

Fig. 5. No significant relationships between drug holidays and the development of ARONJ

Independent variable	P value
Age ≥ 74	0.04
Sex	0.59
Drug holiday	0.38
Steroid therapy	0.57
DM	0.97

Table 1. Outcomes of ARONJ patients

ARONJ patient	extracted tooth position	treatment		outcome (timing of confirmed epithelialization)
		irrigation	antibiotics	
#1	25	○	○	3 mo after bony exposure
#2	22-24, 33, 34, 43, 45	○	○	20 mo after bony exposure
#3	11, 21, 22, 34, 44	○	○	○ (bony exposure for 1.5 mo) 7 mo after bone osteoplasty
#4	11, 21	○	○	○ (continuous socket pain for 3 mo) 4 mo after surgical curettage, confirmed with X-ray
#5	45	○	○	3 mo after bony exposure
#6	15, 16, 48	○	○	○ (bony exposure for 1 mo) 4 mo after bony osteoplasty
#7	26	○	○	3 mo after bony exposure
#8	11, 21, 34, 45, 46, 47	○	○	○ (bony exposure for 5 mo) 2 mo after bony osteoplasty
#9	35	○	○	○ (bony exposure for 3 mo) 1 mo after bony osteoplasty

Discussions

Our study showed higher rate of the development of ARONJ than conventional studies. This higher rate might be responsible for including patients with the temporal bony exposure after tooth extraction, so we need to assess the socket healing thoroughly.

Every ARONJ patient was able to be well-controlled by minimally invasive surgical procedure.

Regarding drug holidays, our study showed eight in nine patients underwent drug holidays before tooth extraction, however statistical analysis showed no significant relationships between taking drug holidays and the development of ARONJ.

Since our study contained a limited number of patients (n=172) and these data came from retrospective study, additional study including prospective study should be required with more patients to elucidate the relationships between taking drug holidays and the development of ARONJ.

Conclusions

Our study suggested that taking drug holidays before tooth extraction was not recommended to reduce the risk of ARONJ.

Since we experienced a patient with compression fracture during drug holidays, we should take them into consideration carefully in managing those patients receiving BPs.

Furthermore, we sometimes experienced patients taking drug holidays before tooth extractions with their own decision or by suggestions from their physicians.

In order to prevent patients from taking drug holidays unintentionally, we should help patients receiving BPs understand the risks of the development of ARONJ, and should continue to cooperate with their physicians to manage appropriate BP treatment.