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ORIGINAL ARTICLE

Dental treatments, tooth extractions, and osteonecrosis of the jaw in Japanese patients with rheumatoid arthritis: results from the IORRA cohort study

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Abstract This study aimed to evaluate dental treatments, tooth extractions, and osteonecrosis of the jaw (ONJ) in Japanese patients with rheumatoid arthritis (RA). Patients with RA enrolled in our cohort completed self-administered questionnaires, which included questions regarding their dental treatments, tooth extractions by dentists during the past 6 months, and past history of ONJ. The history of ONJ was validated with the patients' medical records. Logistic regression was used to determine the association of variables with dental treatments and tooth extractions during the past 6 months. Among 5695 Japanese patients with RA who responded to the questionnaires (mean age, 61.0 years; 85.6 % female), 2323 patients (40.8 %) and 378 patients (6.6 %) reported having had dental treatments and tooth extractions performed by a dentist within the past 6 months, respectively. In multivariate models, advanced age was significantly ($P < 0.0001$) associated with both dental treatments and tooth extractions during the prior 6-month period, and ever smoking was significantly ($P = 0.023$) correlated with tooth extractions during that time. Among patients who reported a history of ONJ, we confirmed five cases of ONJ with patient medical records. The prevalence of ONJ was 0.094 % among all RA patients and 0.26 % among female RA patients ≥65 years of age ($n = 1888$). Our data suggest that more than a few Japanese patients with RA have dental complications that require care by dentists, and that Japanese rheumatologists and dentists should cooperate to improve dental health in patients with RA.

Keywords Dental health · Japanese · Medication-related osteonecrosis of the jaw (MRONJ) · Rheumatoid arthritis · Tooth extraction

Introduction

The relationship between rheumatoid arthritis (RA) and poor oral health has been recognized for decades, and studies have reported that RA is associated with periodontitis and tooth loss [1–3]. A recent Japanese study showed that periodontitis in treatment-naïve arthralgia patients was significantly associated with arthritis activity and the later need for methotrexate treatment upon diagnosis of RA [4]. Oral health-related quality of life is reportedly poor in patients with RA [5]. Limited data are available with regard to the need for dental treatments and tooth extractions in Japanese patients with RA.

Osteonecrosis of the jaw (ONJ) is also an important issue for Japanese patients with RA, because bisphosphonates [6] are the first-line treatment for osteoporosis in this population, and bisphosphonate use appears to be associated with ONJ [7, 8]. In 2011, the American Dental Association guidelines recognized the low risk of ONJ in patients with osteoporosis, and stated that discontinuation of oral bisphosphonates in these patients was not necessary [9]. However, a recent Japanese study suggested that discontinuation of osteoporosis medications may increase the risk of adverse events and disrupt the management of osteoporosis, while not completely preventing ONJ [10]. In 2014, the American Association of Oral and Maxillofacial Surgeons updated its position paper

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on medication-related ONJ (MRONJ) [11], and this topic has recently become a very important issue for both rheumatologists and dentists. Data in the literature are limited with regard to ONJ, bisphosphonate use, and MRONJ in Japanese patients with RA, although two Japanese patients with RA and ONJ who were treated with oral bisphosphonates have been reported [8].

In a previous work, utilizing data from our Institute of Rheumatology Rheumatoid Arthritis (IORRA) cohort study [12], we reported various clinical characteristics of osteoporosis in Japanese patients with RA [13–17]. The current study aimed to evaluate dental treatments, tooth extractions, and history of ONJ in Japanese patients with RA in our IORRA cohort.

Materials and methods

Patients

The IORRA cohort was established in October 2000 as a single institute-based large observational cohort of Japanese patients with RA at the Institute of Rheumatology, Tokyo Women's Medical University. Details regarding the study's purpose and methodology have been reported previously [12–17]. In the current study, we analyzed data from patients who participated in the 28th IORRA survey in April and May 2014. In brief, patients diagnosed with RA were registered in the IORRA cohort database after informed consent was obtained, and they were required to complete and submit a survey biannually. More than 120 publications have described various characteristics of Japanese patients with RA based on this cohort.

Assessment of dental treatments, tooth extractions, and history of ONJ

In the 28th IORRA survey conducted in April/May 2014, patients were invited to complete four questionnaires that included the following questions: (1) Did you undergo a dental treatment by a dentist during the 6 months from October 2013 through March 2014? (2) If yes, did you have a tooth extraction by a dentist during the 6 months from October 2013 through March 2014? (3) If yes, did your physician or dentist ask you to discontinue your osteoporosis medications at the tooth extraction? (4) Have you ever been diagnosed with ONJ? If yes, when? Patient history of ONJ was validated with the patients' medical records.

Statistical analysis

Chi-square tests and Wilcoxon rank-sum tests were used to compare categorical and continuous variables. Associations of the histories of dental treatments and tooth extractions with patient characteristics were considered in multivariate logistic regression analyses with stepwise selection. Age, gender, body mass index, ever smoking, disease duration of RA, disease activity score 28 (DAS28), Japanese Health Assessment Questionnaire Disability Index (JHAQ-DI), positivity of rheumatoid factor, nonsteroidal anti-inflammatory drug use, disease-modifying anti-rheumatic drug use, methotrexate use, biologics use, glucocorticoid use, and daily prednisolone dose were included in the multivariate analyses. $P < 0.05$ was considered significant. All statistical analyses were conducted with JMP statistical software (Japanese version 7; SAS Institute, NC, USA).

Results

Among 5779 Japanese patients with RA (median age, 61.0 years; female, 85.6 %), 5695 responded to the questionnaire regarding dental treatments and tooth extractions. Of these 5695 patients, 2323 (40.2 %) and 378 (6.5 %) reported having undergone dental treatments and tooth extractions by a dentist during the prior 6 months, respectively. Among 1236 patients with RA who reported taking oral bisphosphonates within the past 6 months, 533 (43.1 %) and 83 (6.7 %) reported having had dental treatments and tooth extractions during that period, respectively. Of the 378 RA patients who underwent tooth extractions during the prior 6 months, 83 patients (22.0 %) reported receiving oral bisphosphonates during that period. Among those who received oral bisphosphonates, 55 patients (66.3 %) had been asked by their physicians or dentists to discontinue oral bisphosphonate use.

Demographic and disease-specific characteristics of patients who reported having and not having dental treatments and tooth extractions during the prior 6-month period are shown in Table 1. Patients who underwent dental treatments were significantly older ($P < 0.0001$), had longer RA disease duration ($P = 0.002$), had higher DAS 28 ($P = 0.001$), JHAQ-DI ($P < 0.0001$), patient pain VAS ($P = 0.0008$), and patient general VAS ($P = 0.0002$), tended to take glucocorticoids ($P = 0.016$), and had higher daily prednisolone dosages ($P = 0.039$) compared with those who had not undergone dental treatments. Patients who had tooth extractions were significantly older ($P < 0.0001$), tended to be ever smokers ($P = 0.034$), had longer RA disease duration ($P = 0.0097$), and had higher DAS 28 ($P = 0.019$), JHAQ-DI ($P = 0.0087$), and patient general VAS ($P = 0.038$) compared with those without tooth extractions.

Table 2 shows the results of dental treatments and tooth extractions during the prior 6 months by age and gender.

Table 1 Characteristics of Japanese patients with rheumatoid arthritis: total study population and patients who did and did not have dental treatments during the prior 6 months

Characteristic	With dental treatments $n = 2323$	Without dental treatments $n = 3372$	With tooth extractions $n = 378$	Without tooth extractions $n = 5317$
Sociodemographic and health measures				
Age, mean (SD) (years)	62.6 (12.6)*	59.8 (13.5)*	64.4 (12.4)**	60.7 (13.2)**
Women (%)	85.9	85.3	82.8	85.8
BMI, mean (SD) (kg/m^2)	21.4 (3.1)	21.4 (3.2)	21.6 (3.0)	21.3 (3.2)
Ever smoker (%)	32.3	34.2	38.6**	33.1**
Clinical measures				
Disease duration, mean (SD) (years)	15.2 (10.3)*	14.4 (10.2)*	15.7 (9.6)**	14.7 (10.3)**
DAS28, mean (SD)	2.7 (1.1)*	2.6 (1.1)*	2.8 (1.1)**	2.7 (1.1)**
J-HAQ Disability Index (0–3)	0.64 (0.74)*	0.57 (0.71)*	0.73 (0.81)**	0.59 (0.71)**
Patient pain VAS				
Mean (SD) (cm)	2.4 (0.5)*	2.2 (2.4)*	2.4 (2.5)	2.3 (2.4)
Patient general VAS				
Mean (SD) (cm)	2.6 (2.4)*	2.4 (2.4)*	2.7 (2.5)**	2.5 (2.4)**
Physician global VAS				
Mean (SD) (cm)	0.93 (1.2)	0.89 (1.2)	0.89 (1.1)	0.91 (1.2)
RF-positive (>15 IU/mL) (%)	70.4	71.4	69.4	71.1
CRP, mean (SD) (mg/100 mL)	0.40 (0.90)	0.42 (1.06)	0.39 (0.87)	0.41 (1.0)
Medications				
NSAID use (%)	51.3	51.1	54.8	50.9
DMARD use (%)	90.0	90.7	89.1	90.5
MTX use (%)	77.0	78.2	75.7	77.8
Biologic use (%)	18.9	20.7	17.5	20.1
Bisphosphonate use (%)	22.9	20.8	22.0	21.7
Glucocorticoid use (%)	34.0*	30.9*	32.8	32.1
Daily PSL dose				
Mean (SD) (mg/day)	1.4 (2.8)*	1.2 (2.3)*	1.3 (2.5)	1.3 (2.5)
Tooth extraction, n (%)	378 (16.3)	0	378 (100)	0

BMI body mass index, *SD* standard deviation, *DAS28* 28-joint disease activity score, *J-HAQ* Japanese Health Assessment Questionnaire, *VAS* visual analogue scale, *ESR* erythrocyte sedimentation rate, *RF* rheumatoid factor, *CRP* C-reactive protein, *NSAID* non-steroidal anti-inflammatory drug, *DMARD* disease-modifying anti-rheumatic drug, *MTX* methotrexate, *PSL* prednisolone

* $P < 0.05$, with versus without dental treatment

** $P < 0.05$, with versus without tooth extraction

Table 2 Number (%) of patients with dental treatments and tooth extractions during the prior 6 months by age and gender among Japanese men and women with rheumatoid arthritis

Age (years)	Male (*n*)	Dental treatments	Tooth extractions	Female (*n*)	Dental treatments	Tooth extractions
<50	116	34 (29.3 %)	5 (4.4 %)	1069	357 (33.4 %)	41 (3.8 %)
50s	160	51 (31.9 %)	14 (8.8 %)	1022	383 (37.5 %)	61 (6.0 %)
60s	255	100 (39.2 %)	15 (5.9 %)	1503	631 (42.0 %)	89 (5.9 %)
70s	233	113 (48.5 %)	26 (11.2 %)	1050	525 (50.0 %)	106 (10.1 %)
≥80	56	29 (51.8 %)	5 (8.9 %)	231	100 (43.3 %)	16 (6.9 %)
Total	820	327 (39.9 %)	65 (7.9 %)	4875	1996 (40.9 %)	313 (6.4 %)

Among men with RA, older patients tended to have dental treatments, and patients in their 70s tended to have tooth extractions. Among women with RA, patients in their 70s had a greater tendency to have a history of dental treatments ($P < 0.001$) and tooth extractions ($P < 0.001$) during the prior 6 months than patients in their 60s.

Table 3 Multivariate associations of patient characteristics with dental treatments and tooth extractions by a dentist during the prior 6 months in Japanese patients with rheumatoid arthritis: stepwise regression model

Variable	Dental treatments		Tooth extractions	
	Odds ratio (95 % CI)	*P* value	Odds ratio (95 % CI)	*P* value
Age, per 10 years	1.17 (1.12, 1.22)	<0.0001	1.23 (1.12, 1.35)	<0.0001
Ever smoking	0.93 (0.83, 1.04)	0.20	1.30 (1.04, 1.62)	0.023
J-HAQ Disability Index	1.07 (0.99, 1.15)	0.10	1.14 (0.98, 1.31)	0.086

J-HAQ Japanese Health Assessment Questionnaire, *CI* confidence interval

Table 4 Clinical characteristics of five Japanese patients with rheumatoid arthritis and osteonecrosis of the jaw (ONJ) at the diagnosis of ONJ

Age (years)	Gender	RA disease duration (years)	Location	BP therapy duration (years)	Combined disease	Daily PSL dose
79	Female	17 years	Mandible	Minodronate 7 years	Hypertension	5 mg/day
65	Female	33 years	Mandible	Risedronate 8 years	Diabetes mellitus Hypertension	6 mg/day
77	Female	27 years	Mandible	Alendronate 5 years	Unknown	5 mg/day
79	Female	22 years	Mandible	Until last year Unknown	Chronic kidney disease	No use
77	Female	17 years	Maxilla	Minodronate 5 years	Diabetes mellitus Hypertension	1 mg/day

RA rheumatoid arthritis, *BP* bisphosphonate, *PSL* prednisolone

Table 3 shows the results of the multivariate models. Advanced age was significantly associated with both dental treatments and tooth extractions during the prior 6 months, and ever smoking was significantly correlated with history of tooth extractions during the prior 6-month period. The JHAQ-DI appeared to be associated with both dental treatments and tooth extractions, although the correlations were not statistically significant.

Among the 5779 patients, 5318 answered the questionnaire about the ONJ, and 25 patients reported a history of ONJ. Among these, we confirmed ONJ in five patients and sinusitis in three patients from their medical records, but we found no mention of ONJ or other dental diseases in the medical records of the remaining 17 patients. The five patients with confirmed ONJ were all women >65 years of age, and four were treated with oral bisphosphonates and prednisolone upon diagnosis of ONJ (Table 4). The prevalence of ONJ was 0.094 % among all patients with RA [14] and 0.26 % among female patients with RA ≥65 years of age ($n = 1888$).

Discussion

In this study, we evaluated dental treatments, tooth extractions, and history of ONJ in Japanese patients with RA. To the best of our knowledge, this is the first epidemiological study to investigate the oral health of Japanese patients with RA. Among this group, 40.8 and 6.5 % had undergone dental treatments and tooth extractions, respectively, during the prior 6 months. Advanced age was significantly associated with both dental treatments and tooth extractions, and ever smoking was significantly correlated with tooth extractions during this 6-month period. The prevalence of ONJ in Japanese patients with RA was 0.094 %.

Among the Japanese patients with RA in our cohort, two of five had undergone dental treatments and one of 15 had undergone tooth extraction during the prior 6 months. Studies have reported that patients with long-standing active RA have a significantly higher incidence of periodontitis compared with healthy subjects [1], and that patients with periodontitis have a higher prevalence of RA than patients without periodontitis [18]. More advanced forms of periodontitis were found in patients with early RA compared with controls [2]. A recent Japanese study showed that periodontitis in treatment-naïve arthralgia patients was significantly associated with arthritis activity and the later need for methotrexate treatment upon diagnosis of RA [4]. RA has also been associated with tooth loss and periodontitis [3], and oral health-related quality of life is reported to be poor in patients with RA [5]. Patients with RA have impaired hand function that compromises tooth brushing, and thus these disabilities may be associated with poor dental health and periodontitis. Twenty-eight percent of

patients with RA reported having at least one sicca symptom [19], and RA was diagnosed in 39 % of Japanese patients with secondary Sjögren's syndrome [20]. Thus, periodontitis, difficulty with tooth brushing, and sicca syndrome may be associated with poor dental health in Japanese patients with RA, although further studies are needed to draw firm conclusions.

In this study, advanced age was significantly associated with both dental treatments and tooth extractions in Japanese patients with RA (Table 3). Advanced age has been reported to be associated with tooth loss among the general population, and has been shown to be associated with a risk of periodontitis in patients with RA [21]. In addition, aging has been associated with reduced salivary flow rate in Japanese individuals [22]. Our study thus confirms the association between advanced age and tooth loss in Japanese patients with RA, and periodontitis and sicca syndrome may relate to tooth loss in elderly Japanese patients with RA.

Our data show that ever smoking was significantly correlated with a history of tooth extraction in Japanese patients with RA (Table 3). Smoking status has been found to be correlated with tooth loss in Japanese individuals [23], and both smoking and poor oral health habits are known to increase the risk of periodontitis [24]. Our data confirm the association between smoking and tooth loss in Japanese patients with RA.

Among the patients analyzed, five had a history of ONJ (Table 4). The prevalence (0.094 %) appears to be slightly higher in Japanese patients with RA, because the general prevalence of ONJ among patients who are prescribed oral bisphosphonates for the treatment of osteoporosis ranges from 0 to 0.04 %, with the majority below 0.001 % [25]. Nomura et al. reported clinical characteristics of 13 Japanese patients with ONJ, among which two (15 %) had RA [8]. Several other case reports have discussed patients with RA complicated by ONJ, and suggested a possible association between RA and ONJ [26]. On the other hand, Lecaille and colleagues evaluated the clinical characteristics of ONJ and reported no significant differences between patients with RA and others [27]. Thus, further prospective studies are necessary to clarify the correlation between RA and ONJ.

The Japanese patients with RA who had a history of ONJ were all women over 65 years of age with a long duration of RA; four (80 %) were receiving oral glucocorticoids, and most tended to have other complications such as diabetes (Table 4). Conte-Neto and colleagues reported that patients with RA who develop ONJ are usually women over the age of 60 years who are taking steroids and receiving long-term bisphosphonate therapy [7]. Nomura reported two female Japanese patients with RA with ONJ, and both were over 70 years of age and were taking glucocorticoids [8]. Our study confirms these clinical characteristics [7, 8] in our Japanese patients with RA. Our data suggest that Japanese rheumatologists and dentists may stop treatment with bisphosphonates before tooth extraction, and recognize patients with RA as being at high risk of ONJ if they are elderly woman who are glucocorticoid users and have comorbid diseases like diabetes. Our results also suggest that all patients with RA should receive dental care before starting therapy with antiresorptive agents, because jawbone necrosis is an extremely serious complication and affects many patients, and tooth extraction is closely associated with the onset of MRONJ [11].

Among the patients who required tooth extractions and were receiving oral bisphosphonates, one-third were not asked to discontinue bisphosphonates by their physicians or dentists. Of the five patients with ONJ, one patient had not been taking bisphosphonates until the previous year (Table 4). Taguchi and colleagues recently suggested that discontinuation of osteoporosis medications may increase the risk of adverse events and disrupt the management of osteoporosis, while not completely preventing ONJ [10]. We partially confirmed the results of their study [10] in our Japanese patients with RA, although we did not collect data regarding adverse events after the discontinuation in this study.

Although this was a large cross-sectional study in Japanese patients with RA, it does have several limitations. First, we did not evaluate periodontitis, since we did not collect data regarding periodontitis in this study. Second, we did not validate 17 patients with ONJ who reported having a history of ONJ, because we found no mention of ONJ in their medical records. Third, in four patients we found no trigger events for ONJ, although ONJ occurred after tooth extraction in one patient. We did not interview patients by telephone to confirm ONJ due to the privacy policy in our clinic. We should have used other validation methods to reduce the number of unconfirmed reports of ONJ and ONJ trigger events. Fourth, we did not exclude preventive treatments such as dental scaling from the list of dental treatments. Thus, we may have overestimated the number of dental treatments performed by dentists in this study. Fifth, we did not collect data regarding the specific osteoporosis medications that were discontinued at the tooth extraction, although we collected and analyzed the data regarding the medications that patients took during the prior 6-month period. Sixth, we did not compare our data with those from populations without RA or individuals with other diseases, because we were unable to find any published data regarding dental treatments and tooth extractions in the Japanese population. Seventh, this was a cross-sectional study. Thus, prospective studies are needed to draw firm conclusions. Finally, IORRA is a single institute-based cohort study, so the results may not be generalizable to all Japanese patients with RA.

In conclusion, this study is the first to evaluate the history of dental treatments and tooth extractions in Japanese patients with RA. Our data suggest that more than a few

Japanese patients with RA have dental complications that require care by dentists, and that Japanese rheumatologists and dentists should work in cooperation to improve dental health in patients with RA.

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Compliance with ethical standards

Conflict of interest S. Momohara has received honoraria for speaking and/or unrestricted research grants from AbbVie, Inc.; Asahi Kasei Pharma Corp.; Bristol-Myers Squibb Co.; Chugai Pharmaceutical Co.; Daiichi Sankyo Co., Ltd.; Eisai Co., Ltd.; Mitsubishi Tanabe Pharma Co.; Nakashima Medical Co., Ltd.; Santen Pharmaceutical Co., Ltd.; Taisho Toyama Pharmaceutical Co. Ltd.; and Takeda Pharmaceutical Co., Ltd. H. Y. has received research grants from Abbott, AbbVie, Asahikasei, Astellas, AstraZeneca, Bristol-Myers Squib, Chugai, Daiichi Sankyo, Eisai, GlaxoSmithKline, Janssen, Mitsubishi Tanabe, MSD, Nippon Kayaku, Pfizer, Santen, Taishotoyama, Takeda, and Teijin; has received consulting fees from Abbott, AbbVie, Astellas, AstraZeneca, Bristol-Myers Squib, Chugai, Daiichi Sankyo, Eisai, Mitsubishi Tanabe, Nippon Kayaku, Pfizer, Takeda, and Teijin; and has participated in speakers bureaus for Abbott, AbbVie, Astellas, Bristol-Myers Squib, Chugai, Eisai, Mitsubishi Tanabe, Pfizer, Takeda, and Teijin. The sponsors were not involved in the study design; collection, analysis, or interpretation of data; writing of the paper; or decision to submit for publication. The remaining authors have no conflict of interest to declare.

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