Population-based survey of antimycobacterial drug use among patients with non-tuberculosis mycobacterial pulmonary disease

To the Editor:

Macrolides are key drugs used to treat *Mycobacterium avium* complex (MAC) pulmonary disease (PD) [1, 2]. Members of this complex are the most frequently isolated mycobacterial species in many countries, including Japan [3], where 93.3% of nontuberculosis mycobacterial (NTM)-PDs are due to MAC [4]. The emergence of macrolide-resistant MAC, which has likely been induced by inappropriate treatment, (*e.g.* macrolide-containing regimens without appropriate companion medications and macrolide monotherapy), constitutes a serious challenge to MAC-PD patients, such as prolonged treatment duration and high mortality rate [5, 6]. However, little is known about the treatment practices of MAC-PD patients, especially inappropriate nonstandard treatment. Thus, we conducted a population-based cross-sectional study to describe antibiotic use among NTM-PD patients in Japan.

We used the Japanese national database (NDB), which collects nationwide data for all medical claims from public and private hospitals, pharmacies, and clinics in Japan, and electronically records all medical practices involving payment, such as diagnosis and the prescription of medications. We extracted from the NDB the claims of all individuals with ICD10 codes associated with NTM-PD (A310 and A319) in both in and outpatient claims between September 2009 and December 2014. Then, we defined and identified the incident NTM-PD patients as aged ⩾40 years in 2011 who: 1) had not been issued any claims from September 2009 to December 2010; 2) had been issued at least five claims for NTM-PD between January 2011 and December 2014, with at least one issued in 2011; and 3) had been issued the claims for ⩾24 months. Because most NTM-PD patients in Japan have MAC-PD, as mentioned above, and since claim data do not contain strain information, we used NTM-PD as a proxy for MAC-PD.

To evaluate antibiotics use, patients were classified as one of the following: "standard treatment" patients, who had received 1) macrolide and rifamycin and ethambutol, or 2) macrolide and ethambutol; "nonstandard treatment" patients, who had received the following regimens that diverge from guideline recommendations, 1) only macrolides, 2) macrolides and rifamycin, or 3) macrolides and fluoroquinolone; and "nontreatment" patients, who had not received any of the above treatments. Nonstandard treatment was basically defined as inappropriate treatment without ethambutol based on the findings of previous studies [5, 6]. Antibiotic use of any duration was included. We summarised patients' characteristics in each treatment category with respect to sex, age and comorbidities. We performed univariate and multivariate logistic regression to determine the factors associated with nonstandard treatment using standard treatment as the baseline. The model results are presented as unadjusted and adjusted odds ratios with 95% confidence intervals. The study protocol was approved by the Institutional Review Board of the Research Institute of Tuberculosis, Tokyo (RIT/IRB25-17) and Fukujuji Hospital, Tokyo (Fukujuji/IRB14005).

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This report shows poor adherence to the recommended treatment regimen for NTM-PD patients, which may pose a potential risk for the development of macrolide resistance. The risk was highest among elderly patients, and those with rheumatoid arthritis and COPD. http://bit.ly/3aBoUzE

We identified 22 664 incident NTM-PD patients who met the aforementioned criteria. Of these patients, 6971 (30.8%) had received standard treatment; 8460 (37.3%) had received nonstandard treatment, representing 54.8% of all treated patients; and 7233 (31.9%) had not received treatment. More female patients received treatment (n=16 201; standard treatment 31.7%, nonstandard treatment 37.7%, nontreatment 30.7%) than male patients (n=6463; standard treatment 28.4%, nonstandard treatment 36.5%, nontreatment 35.1%).

The proportion of patients treated with nonstandard treatment continuously increased with increasing age (26.5% at 40–49 years, 32.0% at 50–59 years, 33.6% at 60–69 years, 38.7% at 70–79 years and 44.9% at ⩾80 years) while the proportion of patients treated with standard treatment decreased over the same age groups (39.5%, 38.5%, 34.6%, 29.4% and 21.9% respectively). The proportion of patients who did not receive treatment remained relatively stable with age in all age groups (34.0%, 29.6%, 31.7%, 31.9% and 33.2%).

In the univariate analyses, the factors that were significantly associated with nonstandard treatment included male sex, age ⩾50 years (when compared with age 40–49 years), and having rheumatoid arthritis (RA), chronic obstructive pulmonary disease (COPD), sequelae of pulmonary tuberculosis and interstitial pneumonia (table 1). After adjustment, the factors age ⩾50 years, and having RA and COPD remained significantly associated with nonstandard treatment.

One-third of the patients with incident NTM-PD were observed to be undertreated with antimycobacterial drugs. This may reflect the predominance of nodular/bronchiectatic disease among NTM-PD patients in Japan, which may drive the high proportion of mild diseases and, therefore, the low percentage of patients

TABLE 1 The demographic and clinical factors associated with nonstandard treatment

Variable	Total patients with standard and nonstandard treatment (N=15 431)	Patients with nonstandard treatment (N=8460)	Univariate analysis		Multivariate analysis	
			OR (95% CI)	p-value	aOR (95% CI)	p-value
Sex						
Males	4197	2359 (56.2%)	Ref.		Ref.	
Females	11 234	6101 (54.3%)	0.93 (0.86–0.99)	0.035	0.98 (0.91–1.06)	0.640
Age years						
40–49	520	209 (40.2%)	Ref.		Ref.	
50–59	1798	816 (45.4%)	1.24 (1.01–1.51)	0.036	1.23 (1.01–1.5)	0.044
60–69	4444	2188 (49.2%)	1.44 (1.2–1.74)	<0.001	1.42 (1.18–1.71)	<0.001
70–79	5568	3162 (56.8%)	1.96 (1.63–2.35)	<0.001	1.92 (1.6–2.31)	<0.001
⩾80	3101	2085 (67.2%)	3.05 (2.52–3.7)	<0.001	3.01 (2.49–3.65)	<0.001
Comorbidity						
Rheumatoid arthritis						
No	13 998	7591 (54.2%)	Ref.		Ref.	
Yes	1433	869 (60.6%)	1.30 (1.16–1.45)	<0.001	1.36 (1.21–1.53)	<0.001
Bronchiectasis						
No	11 664	6380 (54.7%)	Ref.		Ref.	
Yes	3767	2080 (55.2%)	1.02 (0.95–1.1)	0.579	1.02 (0.95–1.1)	0.618
COPD						
No	14 350	7783 (54.2%)	Ref.		Ref.	
Yes	1081	677 (62.6%)	1.41 (1.24–1.61)	<0.001	1.31 (1.14–1.49)	<0.001
Sequelae of pulmonary TB						
No	14 628	7988 (54.6%)	Ref.		Ref.	
Yes	803	472 (58.8%)	1.19 (1.03–1.37)	0.021	1.02 (0.88–1.18)	0.828
Interstitial pneumonia						
No	14 038	7655 (54.5%)	Ref.		Ref.	
Yes	1393	805 (57.8%)	1.14 (1.02–1.28)	0.020	1.02 (0.91–1.15)	0.732

Patients who did not receive treatment were excluded from the regression analysis. International Classification of Diseases 10 codes for aspergillosis (B487, B449 and B441), rheumatoid arthritis (M0510, M0530, M0590, M0600, M0690, M0691, M0692, M0693, M0694, M0695, M0696, M0697, M0698 and M0800), bronchiectasis (J47, A162 and Q334), COPD (J449), sequelae of pulmonary tuberculosis (TB) (B909), lung cancer (C340, C341, C342, C343, C349, C780, C795 and Z122), interstitial pneumonia (J704, J841, J849, M0510, M330, M321, M332 and M351) and diabetes mellitus (E10 and E11). To ensure the specificity of comorbidities, a comorbidity was identified when at least five associated claims were made. aOR: adjusted odds ratio; Ref.: reference. p<0.05 was considered statistically significant.

receiving treatment [7]. Although all three drugs used in standard treatment have been covered by Japanese health insurance since 2009, many patients had been treated with nonstandard treatment. Such treatment may pose a potential risk for the development of macrolide resistance [5, 6]. This poor adherence to the recommended regimen was similar to the findings in the USA [8]. We showed the risk of nonstandard treatment was particularly prominent among elderly patients who could not probably comply with the standard treatment due to side-effects. RA and COPD were significant risk factors for receiving nonstandard treatment, implying that those patients may be intolerant to a three-drug regimen.

Some limitations may have biased the results of this study. Because the American Thoracic Society/ Infectious Diseases Society of America diagnostic criteria could not be met due to the unavailability of bacteriological and clinical information, we may have overestimated the number of patients. However, it is also possible that we slightly underestimated the true number of patients, since we defined a case when at least five claims were made, the resulting estimates seem conservative relative to those of previous studies [9–11]. A short course of macrolide monotherapy may also have been provided to treat the common cold among untreated NTM-PD patients, which may have increased the proportion of nonstandard treatment use identified in our study because a minimum duration of treatment could not be considered for the treatment definition due to data analytic limitations. However, the risk of macrolide resistance associated with a very short course of macrolide monotherapy in patients with MAC-PD is unknown.

This is the first study to describe the current status of antibiotic use among NTM-PD patients in Japan and to examine the risk factors for receiving nonstandard treatment using the data covering the entire Japanese population. We identified a significant number of patients who received inappropriate treatments, which could potentially induce macrolide resistance. Macrolide-resistant NTM-PD can increase the patient care needed and healthcare-related costs [9]. Although the use of modified regimens, particularly for elderly patients, is unavoidable, inappropriate treatment should be minimised by enhancing the awareness of guideline-recommended treatment and promoting adherence to treatment, especially elderly patients with comorbidities. More detail on treatments including the duration of therapies and transitions between regimens require study to better understand the magnitude of gaps in practice patterns.

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