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Clinical Evaluation of Macrolide-Resistant *Mycoplasma pneumoniae*

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Macrolide-resistant *Mycoplasma pneumoniae* (MR *M. pneumoniae*) has been isolated from clinical specimens in Japan since 2000. A comparative study was carried out to determine whether or not macrolides are effective in treating patients infected with MR *M. pneumoniae*. The clinical courses of 11 patients with MR *M. pneumoniae* infection (MR patients) treated with macrolides were compared with those of 26 patients with macrolide-susceptible *M. pneumoniae* infection (MS patients). The total febrile days and the number of febrile days during macrolide administration were longer in the MR patients than in the MS patients (median of 8 days versus median of 5 days [$P = 0.019$] and 3 days versus 1 day [$P = 0.002$], respectively). In addition, the MR patients were more likely than the MS patients to have had a change of the initially prescribed macrolide to another antimicrobial agent (63.6% versus 3.8%; odds ratio, 43.8; $P < 0.001$), which might reflect the pediatrician's judgment that the initially prescribed macrolide was not sufficiently effective in these patients. Despite the fact that the febrile period was prolonged in MR patients given macrolides, the fever resolved even when the initial prescription was not changed. These results show that macrolides are certainly less effective in MR patients.

Mycoplasma pneumoniae is a common pathogen causing community-acquired respiratory tract infection mainly in children and young adults. Macrolides are generally considered to be the first-choice agents for treatment of *M. pneumoniae* infection. Although tetracyclines and fluoroquinolones are effective against *M. pneumoniae*, these agents are not recommended for children because of their toxicity. Tetracyclines can cause depression of bone growth, permanent gray-brown discoloration of the teeth, and enamel hypoplasia when given during tooth development. Although the clinical importance of fluoroquinolones has not been demonstrated, they produce cartilage erosion in young animals. Thus, these agents should be given only when there is no alternative (15).

As reported by Lucier et al. (9) and Okazaki et al. (14), an A-to-G transition or A-to-C transversion at position 2063 or 2064 of domain V of the *M. pneumoniae* 23S rRNA gene results in resistance to macrolide antibiotics. We have previously reported the isolation of macrolide-resistant (MR) *M. pneumoniae* from ca. 20% of clinical specimens collected from pediatric patients in Japan (11). Most of those isolates were highly resistant to 14-membered ring macrolides (MIC, >256 μg/ml) and moderately resistant to 15- and 16-membered ring macrolides.

Even in the cases of patients infected with MR *M. pneumoniae*, some pediatricians had the impression that there was a good response to macrolide therapy (11). There is a similar debate about the management of infection due to pneumococci. As noted in The Infectious Diseases Society of America (IDSA) guidelines for community-acquired pneumonia management (10), despite the increase of resistant isolates, a corresponding increase has not been seen in the number of clinical treatment failures.

One possible explanation for this is the nonantimicrobial effects of macrolides. It is known that macrolides have beneficial immunomodulating effects (1, 4, 6, 20), and they are clinically effective in hypersecretory conditions such as diffuse panbronchiolitis (7, 8) and cystic fibrosis (16). Thus, macrolides could be clinically effective even in MR *M. pneumoniae* infections.

It is important to know the clinical significance of MR *M. pneumoniae* infection, because in vitro susceptibility testing for *M. pneumoniae* is not available for daily management of patients. If macrolides are clinically effective against MR *M. pneumoniae* infection, pediatricians do not need to consider the use of tetracyclines or fluoroquinolones, even if the prevalence of MR *M. pneumoniae* rises in the future. Therefore, we performed a comparative study to determine whether or not MR *M. pneumoniae* influences the clinical outcome in patients treated with macrolides.

MATERIALS AND METHODS

Study population and sample collection. Three pediatric clinics in three different areas in Japan participated in this study. Sera and throat swabs or sputa taken from inpatients or outpatients suspected of *M. pneumoniae* infection were subjected to the laboratory tests.

Isolation. Isolation and identification of *M. pneumoniae* was carried out as described in a previous report (11).

PCR detection of *M. pneumoniae*. Sputa were obtained from patients, suspended in a small amount of saline, mixed well, and centrifuged at 2,000 rpm for 15 min, and then DNA was extracted from the supernatant with a QIAamp DNA Mini kit (QIAGEN K. K., Tokyo, Japan) according to the manufacturer's instructions. *M. pneumoniae* DNA was detected by the nested PCR method with primer sets for amplification of the P1 gene as previously described (17). The first

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TABLE 1. Prevalence of macrolide-resistant *M. pneumoniae* in Japan

Year	Isolation method		DNA detection method	
	No. of isolates	No. of resistant isolates (%)	No. of specimens with positive *M. pneumoniae* DNA (no. of examined specimens)	No. of specimens with macrolide resistance mutation in *M. pneumoniae* DNA (%)
1999	296	0	12 (630)	0
2000	10	1 (10.0)	9 (92)	4 (44.4)
2001	6	2 (33.3)	28 (384)	3 (10.7)
2002	12	3 (25.0)	44 (352)	5 (11.4)
2003	54	7 (13.0)	10 (236)	1 (10.0)
2004	6	1 (16.7)	8 (183)	2 (25.0)
5-year total (2000–2004)	88	14 (15.9)	99 (1247)	15 (15.2)

primer set was ADH2F (5′-GGC AGT GGC AGT CAA CAA ACC ACG TAT-3′) and ADH2R (5′-GAA CTT AGC GCC AGC AAC TGC CAT-3′). The second primer set was ADH3F (5′-GAA CCG AAG CGG CTT TGA CCG CAT-3′) and ADH3R (5′-GTT GAC CAT GCC TGA GAA CAG TAA-3′).

Serological diagnosis. Particle agglutination (PA) antibody titers for *M. pneumoniae* were assayed by using Serodia-MYCO II (Fuji Rebio Ltd., Tokyo, Japan), which is manufactured using artificial gelatin particles, sensitized with cell membrane components of *M. pneumoniae*, according to the manufacturer's instructions.

Detection of resistance point mutations in domain V of 23S rRNA. MR *M. pneumoniae* isolates were screened on the basis of MIC of erythromycin (ERY), and identification of point mutations in domain V of 23S rRNA for ERY-resistant *M. pneumoniae* was performed according to our previously reported methods (11). For PCR-positive samples of *M. pneumoniae* DNA, the detection of a point mutation is indicative of a resistant phenotype because there is only a single rRNA operon in the genome (2). Neither plasmids with *erm* genes to mediate ribosomal modification nor any enzymes that inactivate macrolides have been found in *M. pneumoniae*. Thus, the prevalence of MR *M. pneumoniae* detected by the PCR methodology should reflect the true incidence of resistant strains.

Patient extraction for comparison of clinical courses. Clinical information was collected for the patients from whom *M. pneumoniae* had been isolated or its DNA detected. Patients who fulfilled the following criteria were extracted: (i) *M. pneumoniae* infection was laboratory confirmed, (ii) macrolides were prescribed during the illness, and (iii) complete information about prescribed antimicrobial agents and febrile days was available from the medical record. Laboratory-confirmed *M. pneumoniae* infection was defined as (1-a) isolation of *M. pneumonia*e from throat swabs or (1-b) detection of *M. pneumoniae* DNA from the sputum by PCR methods and serologically positive results, i.e., fourfold or greater rise of antibody titer in paired serum samples or titer higher than 1:640 in a single-serum sample by PA assay.

Patients infected with *M. pneumoniae* showing a point mutation in domain V of the 23S rRNA gene were defined as MR *M. pneumoniae*-infected patients (MR patients), and those infected with *M. pneumoniae* without the mutation were defined as macrolide-susceptible *M. pneumoniae*-infected patients (MS patients). MS patients were selected from the same study population as MR patients, and there were approximately twice as many of them as MR patients.

Measurement of clinical efficacy. To compare the clinical courses of MR and MS patients, we adopted the number of febrile days as a main outcome measurement. A febrile day was defined as a day during which the body temperature exceeded 38.0°C at least once. Total febrile days and the number of febrile days during macrolide administration were assessed. As these parameters would be affected by the time of commencement of macrolide administration, the number of febrile days before macrolide administration was also assessed. Other clinical symptoms and signs, such as cough and chest roentgenogram findings, were not taken into account in this study on account of the difficulty of objective and unified assessment through a retrospective review of medical records.

The numbers of patients whose prescribed antibiotic was changed were also compared. We speculated that a change in prescribed antimicrobial agent might reflect the pediatrician's clinical decision that the initial therapy had insufficient efficacy based on the general clinical condition of the patients. The pediatricians had no information about the susceptibility of *M. pneumoniae* at the time of clinical decision-making.

TABLE 2. Characteristics of enrolled patients

Characteristic	MR patients (n = 11)	MS patients (n = 26)	P
Age (yr)			
Median (range)	9.0 (0–13)	5.5 (1–14)	0.30
Mean	7.6	6.5	
Sex, male/female	4/7	14/12	0.33
No. of patients prescribed 14-membered ring macrolides (%)	8 (72.7)	7 (26.9)	0.025

Statistical analysis was performed using SPSS software, version 9.05 for Windows (SPSS, Inc., Chicago). Differences in categorical variables were assessed with the two-tailed Fisher's test, and for the comparison of medians the exact Wilcoxon rank-sum test was used. P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

Prevalence of MR *M. pneumoniae*. The prevalence of MR *M. pneumoniae* among clinical isolates and specimens with positive *M. pneumoniae* DNA is shown in Table 1. Before 1999, no MR *M. pneumoniae* was found among 296 clinical isolates. In 2000, however, MR *M. pneumoniae* appeared in 10% of isolates, and its prevalence rose to 33.3% in 2001. The overall prevalence of MR *M. pneumoniae* during 2000 to 2004 was 15.9%. All MR *M. pneumoniae* isolates had a resistance point mutation in domain V of 23S rRNA. A similar trend was seen in specimens with PCR-positive *M. pneumoniae*. Although the number of positive specimens before 1999 was limited (n = 12), no MR *M. pneumoniae* was detected. The prevalence of MR *M. pneumoniae* during 2000 to 2004, based on PCR-positive specimens, was 15.2%.

Comparison of the clinical courses between MR and MS patients. Eleven MR patients were selected for the analysis according to the criteria given above, and 26 MS patients were used as controls.

The patients' characteristics are summarized in Table 2. All patients were outpatients at the time of onset and had no severe underlying disease that might have influenced the clinical course. MR patients tended to be older and had a lower male/female ratio than MS patients, but the differences lacked statistical significance. Most patients were first prescribed β-lactam antimicrobial agents by primary physicians, followed by prescription of macrolides after attendance at a hospital. The prescribed macrolides differed among MR and MS patients. Significantly more MR patients than MS patients were prescribed 14-membered ring macrolides (72.7% versus 26.9%; P = 0.025). The majority of MS patients (19 out of 26 [73.1%]) were prescribed only 15-membered ring macrolides (azithromycin [AZM]).

The clinical courses in the MR and MS patients are summarized in Table 3. The total febrile days and the number of febrile days during macrolide administration were significantly greater in MR patients than in MS patients (median of 8 days versus 5 days [P = 0.019] and 3 days versus 1 day [P = 0.002], respectively). Febrile periods before macrolide administration, which consist of antimicrobial-free and mostly β-lactam-ad-

TABLE 3. Comparison of clinical courses in MR patients and MS patients

Characteristic	MR patients ($n = 11$)	MS patients ($n = 26$)	*P*
Febrile days			
Median (range)	8 (4–19)	5 (2–9)	0.019
Mean	9.3	5.5	
Febrile days during macrolide administration			
Median (range)	3 (1–11)	1 (1–5)	0.002
Mean	4.3	1.4	
Febrile days before macrolide administration			
Median (range)	3 (1–10)	4 (1–8)	0.402
Mean	3.8	4.1	
No. of patients with a febrile period exceeding 48 h after macrolide administration (%)	8 (72.7)	5 (19.2)	0.006
No. of patients with a change of prescription after macrolide administration (%)	7 (63.6)	1 (3.8)	<0.001

TABLE 4. Comparison of patients prescribed 14-membered ring macrolides

Characteristic	MR patients ($n = 8$)	MS patients ($n = 7$)	*P*
Total febrile days			
Median (range)	10.0 (4–19)	6.0 (4–9)	0.152
Mean	10.4	6.6	
Febrile days during macrolide administration			
Median (range)	3.5 (1–11)	1.0 (1–2)	0.004
Mean	4.9	1.1	
Febrile days before macrolide administration			
Median (range)	3.0 (1–10)	5.0 (3–8)	0.152
Mean	4.0	5.4	
No. of patients with a febrile period exceeding 48 h after macrolide administration (%)	7 (87.5)	1 (14.3)	0.01
No. of patients with a change of prescription after macrolide administration (%)	6 (75.0)	0	0.007

ministered days, showed no statistically significant difference (median of 3 days versus 4 days, $P = 0.402$).

The MR patients were more likely to have had the initially prescribed macrolide changed to another antimicrobial agent by their pediatricians (63.6% versus 3.8%; odds ratio, 43.8; $P < 0.001$). Among seven MR patients whose prescriptions were changed, all but one were changed to minocycline.

The results were similar for patients to whom 14-membered ring macrolides were administered (Table 4). Among these 15 patients (8 MR patients and 7 MS patients), 9 patients were prescribed clarithromycin, while the remaining 6 were prescribed ERY. Presumably due to the fact that the number of febrile days during macrolide administration was greater in MR patients than in MS patients (median of 3.5 days versus 1.0 day, $P = 0.004$), the initially prescribed macrolide was more frequently changed among MR patients than MS patients (75% versus 0%, $P = 0.007$). Although there was no statistical significance, there was a prolongation of total febrile days for MR patients (median of 10 days versus 6 days, $P = 0.152$).

When we focused on patients given 15-membered ring macrolides, 2 MR patients and 19 MS patients, the differences were not clear. Although there were only two MR patients in this group, their total febrile days and number of febrile days during macrolide administration were not different from those of MS patients (medians of 4.5 days versus 5.0 days and 1.0 day versus 1.0 day, respectively).

DISCUSSION

There are few reports on the isolation of MR *M. pneumoniae* from clinical specimens, and most of the isolates were obtained following ERY treatment (13, 19). In our survey, MR *M. pneumoniae* was not found in any of 296 clinical isolates or 12 *M. pneumoniae* PCR-positive specimens collected between 1983 and 1999, but it has been found in 15% to 20% of clinical isolates or PCR-positive specimens since 2000. MR *M. pneumoniae* first appeared in 2000 and rapidly spread throughout Japan (11, 12). Thus, it is important to evaluate the clinical significance of MR *M. pneumoniae*.

In our study, when patients infected with MR *M. pneumoniae* were treated with macrolides, the total febrile period was 3 days longer than that of patients with MS *M. pneumoniae*. Although we did not assess other clinical outcome variables, such as chest roentgenogram findings, a higher frequency of changes in prescription was observed in MR patients than in MS patients. This might reflect the pediatrician's judgment, based on the patient's clinical condition, that the initially prescribed macrolide was not sufficiently effective, even though the pediatricians had no information about the susceptibility of isolates at the time of clinical management. This tendency was also seen in patients who were treated only with 14-membered ring macrolides.

It was difficult to assess the immunomodulatory effects of macrolides in patients with *M. pneumoniae* infection in this study, because all the patients enrolled were prescribed macrolides according to the inclusion criteria. To evaluate the immunomodulatory effects of macrolides, it will be necessary to compare the clinical outcomes among MR patients treated with and without macrolides. An alternative is to compare the number of febrile days of MR patients with that of patients without antimicrobial agent therapy in the literature. According to review articles, fever might persist for about a week in the natural course of *M. pneumoniae* infection (3, 18). Kingston et al. (5) evaluated the effect of demethylchlortetracycline in a double-blind study, and the mean duration of fever in the treated group was 2.13 days, while it was 8.14 days in the placebo group. They started to count the number of febrile days not at the point of onset but only after entry into the study. In our study, the mean number of febrile days of MR patients was 9.2, which is similar to that of the placebo group

in Kingston's study. This implies that the antimicrobial effect is dominant over immunomodulatory effects in macrolide therapy, at least as far as duration of fever in *M. pneumoniae* infection is concerned. On the other hand, we did not assess the duration of other symptoms, such as malaise, sore throat, and cough, and it is possible that the immunomodulatory effects of macrolides can shorten these symptoms even in MR *M. pneumoniae* infection.

A difference of three febrile days in MR patients might not have a great impact in the management of *M. pneumoniae* infection, because it is often a mild and self-limiting disease, and the fever resolved even when the initially prescribed macrolide was not changed. However, it is reasonable to consider the use of alternative antimicrobial agents, such as minocycline, when macrolides are less effective than expected in patients more than 8 years old with possible *M. pneumoniae* infection.

The criteria for *M. pneumoniae* infection used in this study were stringent enough to confirm acute *M. pneumoniae* infection. This was a retrospective study based on a review of medical records, and patients with incomplete records were excluded. In general, clinical records of patients showing mild illness with *M. pneumoniae* infection were incomplete, and their clinical evaluation was excluded from this study.

In conclusion, we compared clinical outcomes in 11 MR patients and 26 MS patients given macrolide therapy. The MR patients showed more febrile days (by a median of 2 days) during the initial macrolide therapy than MS patients. On the other hand, no apparent treatment failure or serious illness was reported for MR patients. The influence of the emergence of MR *M. pneumoniae* on the treatment for *M. pneumoniae* infection deserves further study.

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