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【 ORIGINAL ARTICLE 】

Effects of Early Administration of Macrolides on Whooping Cough in Adolescents and Adults: A Single-center Retrospective Cohort Study

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Abstract:

Objective This study aimed to elucidate the effects of early macrolide administration on genetically confirmed pertussis-induced cough in adolescents and adults.

Methods This single-center, retrospective cohort study examined the effects of the early administration of macrolides and antitussive agents on cough secondary to pertussis. We divided the patients into two groups based on the median duration from the beginning of the cough to the initiation of macrolide administration: early macrolide administration group (EMAG) and non-early macrolide administration group (NEMAG). The clinical improvement of cough was defined as maintaining a cough awareness score of ≤3 points for 3 consecutive days.

Patients The medical records of 40 patients diagnosed with pertussis (≥12 years old) who were able to maintain a cough diary and received no other antibiotics aside from macrolides were included in the study. A diagnosis of pertussis was made using the loop-mediated isothermal amplification (LAMP) test.

Results The EMAG (24 patients) showed a significantly shorter total cough period than the NEMAG [16 patients; 20.0 (95% confidence interval (CI), 16-28) vs. 30.5 (95% CI, 27-40) days; log-rank test, p=0.002]. There was no significant difference in the post-administration cough periods between the EMAG and NEMAG [11.0 (95% CI, 7-19) vs. 13.0 (95% CI, 5-23) days; log-rank test, p=0.232]. Antitussive agents did not affect the cough.

Conclusion The early administration of macrolides, but not antitussive agents, is effective for treating pertussis. Therefore, macrolides should be administered as soon as possible for this disease.

Key words: antitussive agents, *Bordetella pertussis*, cough, macrolides, whooping cough

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Introduction

In Japan, since January 2018, all cases of whooping cough have been reported to the public health center; 16,845 cases were reported in 2019 (1). Whooping cough is not a rare disorder. Patients diagnosed with pertussis are expected to experience a prolonged cough and possibly chest pain, difficulty eating, sleep disturbance, and emesis owing to exacerbated strong cough. Infants, particularly those <12 months old, experience serious effects, and the associated mortality rates are high. Worldwide, pertussis was estimated to account for 195,000 deaths in children <5 years old in 2008 (2).

However, not only infants but also adolescents and adults may be seriously affected, requiring hospitalization owing to severe progressive cough with rib fractures and intercostal vessel injuries (3). Since 1980, the incidence of whooping cough in adolescents and adults has increased (4). It is thus a disease that should be considered when a patient, irrespective of their age, complains of a strong cough.

Macrolides are used to treat adolescents and adults, but there are some problems with the rationale behind their use. We believe that two important aspects are involved in treat-

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ing whooping cough: the effectiveness of treatment against cough symptoms and the possibility of control of infection in society via the eradication of *Bordetella pertussis* and the prophylactic administration of the treatment to contacts. Many studies have focused on eradicating *B. pertussis* and preventing its transfer between connections rather than on improving the symptoms (5).

Whooping cough is often diagnosed serologically rather than bacteriologically or genetically. Because the antibody titer does not decrease for several years, a single antibody titer measurement is not sufficient for a definitive diagnosis (6). When confirming the therapeutic effect of macrolides, it is important to have a definitive diagnosis.

A systematic review reported the effects of drug treatment on whooping cough (7). Surprisingly, no previous reports have demonstrated the apparent therapeutic effects of antimicrobial agents on cough in adolescents or adults with a confirmed bacteriological or genetic diagnosis. Antibacterial therapy is necessary to eradicate the bacteria and prevent the societal spread of infection, even if it has a limited effect on cough. Therefore, it is difficult to investigate the effects of drugs against placebo on cough caused by *B. pertussis* infection in prospective studies. We believe that the therapeutic effect of macrolides on the symptoms of adolescents and adults with bacteriologically or genetically confirmed whooping cough can be elucidated by evaluating the effect of early administration.

Therefore, we evaluated the effects of early macrolide administration on genetically confirmed pertussis-induced cough in adolescents and adults.

Materials and Methods

Study design and patients

In this single-center, retrospective cohort study, we extracted the electronic medical records of patients ≥12 years old who presented to our clinic between July 2017 and February 2020 with a chief complaint of a cough and were diagnosed with pertussis based on the findings of the loop-mediated isothermal amplification (LAMP) test. Clinical samples were obtained from the nasopharynx using the FLOQSwabs® (Nippon Becton Dickinson, Tokyo, Japan), and the test was performed in the laboratory of an external testing company (BML, Tokyo, Japan).

We conducted a medical interview to identify the characteristic symptoms of whooping cough. Patients who were able to maintain a diary for monitoring cough and were treated with macrolides were enrolled in this study. Those who were unable to maintain a diary and/or were treated with other antibiotics were excluded. The diary was maintained as follows: The patients recorded their cough awareness score since the visit leading to the diagnosis. Regarding this cough awareness score, the strongest cough the patient felt since the time of diagnosis was assigned 10 points, whereas the absence of cough was assigned 0 points. The cough symptoms were recorded every day in the form of integers (0 to 10). The patients brought their diaries to every visit.

We divided the patients into two groups based on the median duration from the beginning of the cough to the initiation of macrolide administration: early macrolide administration group (EMAG) and non-early macrolide administration group (NEMAG). A total of 40 patients were included in this study. The median duration from the onset of cough to the administration of macrolides was 11 days. This timepoint was used as the cut-off to divide the patients into the EMAG and NEMAG. The details of macrolide treatment are as follows: 400 mg/day of clarithromycin was administered to 33 patients for 10 days, 3 patients for 5 days, 2 patients for 7 days, and 1 patient for 14 days; and 500 mg/day of azithromycin hydrate was administered to 1 patient for 3 days. The primary outcome is the effective reduction of cough period from onset. The clinical improvement of cough was defined as the maintenance of a cough awareness score of ≤3 points for 3 consecutive days.

We also examined the following as secondary outcomes: differences in age, sex, smoking, and culture results between the two groups; differences in the duration of cough after macrolide administration, which was calculated from the date of initiation of macrolide treatment between the two groups; and effects of antitussive agents. We examined the effects of treatment with antitussive agents by dividing the patients into two groups, as with macrolide administration; in detail, we divided the patients into the early and non-early treatment groups based on the median duration from the cough onset to the initiation of antitussive treatment. We compared the total cough period and post-treatment cough period in both groups. The median duration from the onset of cough to the initiation of antitussive treatment was 8 days. Therefore, we used this timepoint as the cut-off to divide the patients into early and non-early antitussive treatment groups. The details of the antitussive treatment were as follows: 32 patients received 90 mg/day of dextromethorphan hydrobromide hydrate, 2 patients received 60 mg/day of tipepidine hibenzate, 2 patients received dihydrocodeine phosphate combination drug, and 1 patient received 30 mg/day of dimemorfan phosphate.

The study protocol was approved by the Japan Medical Association Ethical Review Board. Informed consent was obtained in the form of opt-out by bulletin board in our hospital.

Statistical analyses

All statistical analyses were performed using EZR (8) (Saitama Medical Centre, Jichi Medical University, Saitama, Japan), which is graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions that are frequently used for biostatistical analyses. Continuous variables are presented as medians with interquartile ranges, while categorical variables are

Table 1. Baseline Characteristics.

Characteristics	Early administration† (n=24)	Non-early administration‡ (n=16)	p value
Age, median (IQR)	46 (26.5-61.5)	53 (26.5-72)	0.516
Male sex, n (%)	10 (41.7)	6 (37.5)	0.792
Smoking history			0.277
Current smoker, n (%)	3 (12.5)	0 (0.0)	
Ex-smoker, n (%)	4 (16.7)	5 (31.3)	
Non-smoker (never smoked), n (%)	17 (70.8)	11 (68.8)	
Culture positivity, n (%)	9 (37.5)	6 (40.0)¶	0.876
Macrolide, median (IQR)§	9.5 (7-11)	15.5 (14.5-20)	0.001>
Antitussive, median (IQR)‖	7 (6-10)	12.5 (6.75-20)	0.020

†In this group, macrolides were administered within 11 days after the onset of cough

‡In this group, macrolides were administered over 12 days after the onset of cough

§Days until the initiation of macrolide administration from onset

‖Days until the initiation of antitussive agent use from onset

¶n=15, one patient had not undergone this test

n: number of patients, IQR: interquartile range, Mann-Whitney U test: age, antitussive, Chi-squared test: sex, culture, Fisher test: smoking

Table 2. Characteristic Symptoms of Pertussis Infection.

Characteristic symptoms	Early administration† (n=24)	Non-early administration‡ (n=16)	p value
Whooping, n (%)	4 (16.8)	7 (43.8)	0.080
Paroxysmal cough, n (%)	22 (91.7)	12 (75.0)	0.195
Vomiting and gagging			0.681
Vomiting, n (%)	1 (4.2)	2 (12.5)	
Gagging, n (%)	15 (62.5)	10 (62.5)	
Nothing, n (%)	8 (33.3)	4 (25.0)	
Apnea, n (%)	2 (8.3)	2 (12.5)	1.000

†In this group, macrolides were administered within 11 days after the onset of cough

‡In this group, macrolides were administered over 12 days after the onset of cough

n: number of patients

Fisher test: whooping, paroxysmal cough, vomiting and gagging, apnea

presented as numbers with percentages in parentheses. Regarding the comparison of basic data between two groups, Fisher's test or the chi-squared test was used for categorical variables, and the Mann-Whitney U test was used for continuous variables. We used the Kaplan-Meier log-rank test to estimate the cumulative clinical improvement of the cough.

Results

Study population

There were 24 patients in the EMAG (administered within 11 days after the onset of cough) and 16 patients in the NEMAG. There were no differences in age, sex, smoking history, or culture results between the two groups. There were 8 adolescents (<20 years) and 32 adults (≥20 years). The duration from the onset of cough to the initiation of antitussive treatment was shorter in the EMAG than in the NEMAG (Table 1). There were no marked differences in whooping, vomiting, gagging, paroxysmal coughing, or apnea, which are the characteristic symptoms of whooping cough, between the two groups (Table 2).

Effects of macrolide administration on cough

The Kaplan-Meier analysis showed that the EMAG had a shorter total cough period but not the cough period after macrolide administration than the NEMAG. The median total cough periods in the EMAG and NEMAG were 20.0 [95% confidence interval (CI), 16-28], and 30.5 (95% CI, 27-40; log-rank test p=0.002) days, respectively. Furthermore, the median post-treatment cough periods in the early and non-early administration group were 11.0 (95% CI, 7-19) and 13.0 (95% CI, 5-23; log-rank test p=0.232) days, respectively (Fig. 1). Two (who did not consult the hospital again for unknown reasons) and no patients were censored in the EMAG and NEMAG, respectively.

Effects of antitussive treatment on cough

There were 21 patients in the early antitussive treatment group (administered within 8 days after the onset of cough)

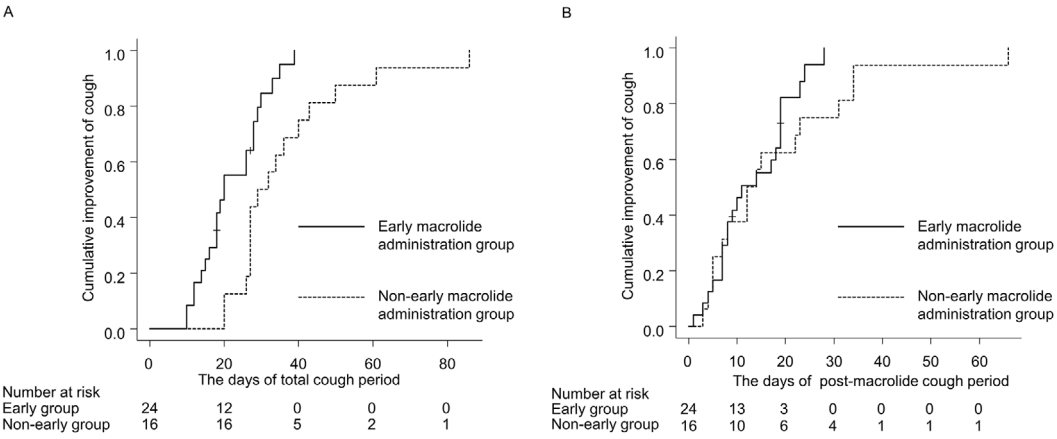

Figure 1. Analyses of the effects of early and non-early macrolide administration on cough duration. The macrolide early administration group (24 patients) was treated ≤11 days after the onset of cough, and the non-early macrolide administration group (16 patients) was treated ≥12 days after the onset of cough. The clinical improvement of cough was defined as the maintenance of a cough awareness score of ≤3 points for 3 consecutive days. Censoring of data is indicated by either vertical or horizontal bars. (A) A comparison of the total cough period between the two groups (primary outcome). Patients in the early and non-early treatment groups had a median cough period of 20.0 [95% confidence interval (CI), 16-28] days and 30.5 (95% CI, 27-40) days, respectively (log-rank test, p=0.002). (B) A comparison of the post-administration cough period between the two groups. No statistically significant differences were detected in the median post-administration cough period between the groups [11 (95% CI, 7-19) days vs. 13 (95% CI, 5-23); log-rank test, p=0.232]. CI: confidence interval

and 19 in the non-early antitussive treatment group. There were no marked differences in the total duration of cough or the duration of cough after antitussive treatment between the early and non-early antitussive treatment groups. The median total cough periods in the early and non-early antitussive treatment group were 27.0 (95% CI, 18-30) and 27.0 (95% CI, 20-33; log-rank test, p=0.547) days, respectively. Furthermore, the median post-treatment cough period in the early and non-early treatment groups was 20.0 (95% CI, 11-24) and 10.0 (95% CI, 7-19; log-rank test, p=0.216) days, respectively (Fig. 2).

Discussion

This is the first study to show that early macrolide administration significantly shortens the total cough period in adolescent and adult patients with genetically confirmed pertussis. Furthermore, this study examined the effects of antitussives. Antitussive treatment was started significantly earlier in the EMAG than in the NEMAG because it is common practice to administer antitussives simultaneously with or prior to macrolides in all cases. However, early antitussive treatment did not help shorten the total duration of cough. Although we must consider the exploratory nature of this study, our findings suggest that pertussis treatment with macrolides shortens the cough period and that treatment with antitussive agents alone may not have this effect.

A previous study evaluated the effect of early administration of erythromycin on whooping cough in 189 children, including 103 subjects <5 years old (9). The median durations of cough and paroxysms were 38 and 28 days, respectively, in the early-treatment group (within 7 days after onset) and 57 and 44 days, respectively, in the late-treatment group (over 21 days after onset). That study included culture-positive cases alone, but the subjects were all children. With regard to the therapeutic effects of macrolides on adults with pertussis, Miyashita et al. (10) reported that the early administration of clarithromycin within 14 days of onset was able to shorten the total cough period. However, they only included nine subjects in their study, and most of these cases were serologically diagnosed; only three cases were diagnosed using polymerase chain reaction (PCR). In our study, the definitive diagnosis was confirmed using the LAMP method, and more cases were included. A previous study with a large study sample reported the effects of early erythromycin administration, regardless of age (4). In that report, when the interval between the onset of cough and the administration of erythromycin was within 7 days, the relative risk of occurrence of cough for ≥28 days was lower in the erythromycin administered group than in the erythromycin non-administered group by 0.81. Over 70% of the subjects in that report were children <9 years old. In addition, the study showed some problems in the evaluation of the therapeutic effect. The early erythromycin administration group showed an interval of 0 days from the administration to the onset, possibly due to prophylactic administration in the household before the onset, which was not mentioned. In addition, the risk ratio of the group in which erythromy-

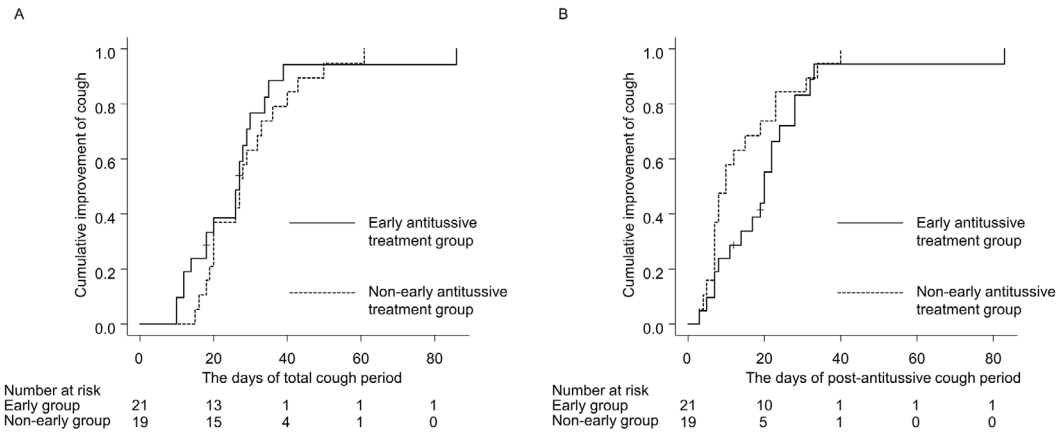

Figure 2. Analyses of the effects of early and non-early antitussive treatment on the cough duration. The early antitussive treatment group administration group (21 patients) was treated ≤8 days after the onset of cough, and the non-early antitussive treatment group (19 patients) was treated ≥9 days after the onset of cough. The clinical improvement of cough was defined as the maintenance of a cough awareness score of ≤3 points for 3 consecutive days. Censoring of data is indicated by either vertical or horizontal bars. (A) A comparison of the total cough period between the two groups. No statistically significant differences were detected in the median cough periods between the two groups [27 (95% CI, 18-30) days vs. 27 (95% CI, 20-33) days; log-rank test, p=0.547]. (B) A comparison of the post-treatment cough period between the two groups. No statistically significant differences were detected between the two groups [20 (95% CI, 11-24) days vs. 10 (95% CI, 7-19); log-rank test, p=0.216]. CI: confidence interval

cin was administered for ≥14 days was significantly higher (1.22) than that in the untreated group, suggesting the involvement of confounding factors other than the therapeutic drug. Our report is different from these previous reports and useful in that it does not discuss prophylactic administration and shows that early macrolide administration is more effective than non-early macrolide administration.

Furthermore, a previous study examined the effect of erythromycin in patients affected by outbreaks in institutions (11). About 50% and 30% of the patients were 10-19 and ≥20 years old, respectively. That study examined and compared the effects of early and late erythromycin administration before or at the onset of symptoms other than a cough in 83 pertussis antibody-positive individuals; 43% (17 of 40) of early-treated patients and 19% (8 of 43) of late-treated patients did not have a cough. Furthermore, early treatment is reported to shorten the duration of cough and reduce the severity of symptoms. However, because the pertussis antibody titer does not decrease for several years (6), upper respiratory tract infections other than pertussis cannot be ruled out, especially in the early treatment group. At present, it is possible to prove the existence of bacteria using genetic methods in addition to bacterial cultures with a low positive rate. It is important to confirm the therapeutic effect of the drug on genetically confirmed whooping cough. Although our study is retrospective, its findings are significant regarding this aspect.

When treating pertussis, assessing the degree of cough is often difficult. Progress of cough can be tracked well by maintaining a diary. Therefore, in our clinic, patients diagnosed with pertussis are asked to maintain a cough diary to confirm the therapeutic effects. We understand that it is difficult to observe acute cough until it disappears completely in the actual clinical setting because patients do not visit the doctor once the symptoms of cough improve to some extent; this is especially true in the case of adolescents and adults compared with children. Furthermore, cough often improves and worsens day by day before being resolved eventually. Therefore, we defined clinical improvement as the maintenance of a cough awareness score of ≤3 points for 3 consecutive days.

For the diagnosis of *B. pertussis* infection, the LAMP method was adopted. The LAMP assay and the conventional single-PCR assay are equally useful for the diagnosis of *B. pertussis* infection (12). LAMP was demonstrated to be more useful for the diagnosis of pertussis than was the culture method (13). In Japan, the LAMP method is widely used as a confirmatory test for diagnosing *B. pertussis* infection (14).

Adolescent and adult patients with whooping cough do not present the typical symptoms like infants, which increases the difficulty of the diagnosis. Poor immunity owing to a prolonged infection or duration since the vaccination may mask the typical symptoms. We were unable to confirm the accurate vaccination history and medical history of our subjects; however, they are considered to have insufficient immunity owing to past illnesses and their vaccination history. This may be why our subjects did not always exhibit characteristic symptoms, especially vomiting and whooping. In adults, the occurrence of whooping or post-tussive vomit-

ing provides a strong basis for suspecting whooping cough, and the lack of paroxysmal cough or the presence of a fever provides a basis for excluding whooping cough (15). We must suspect whooping cough when we treat an acute cough with these characteristics. If whooping cough is suspected, it is important to start macrolide administration as early as possible. Patients desire early relief from a painful cough. By showing the usefulness of early treatment, we can expect the improvement of drug adherence and help control infections at the societal level.

Several limitations associated with the present study warrant mention. We did not rule out other cough-causing infections, respiratory illnesses that cause cough, or the effects of antitussives. Furthermore, the dose and duration of macrolide administration varied among patients. Therefore, a further prospective study with similar conditions between groups and strict exclusion of respiratory diseases that cause cough is warranted.

In conclusion, this study showed early macrolide administration to be useful for the treatment of genetically diagnosed whooping cough in adolescents and adults. We should consider initiating the administration of macrolides along with antitussive agents rather than that of antitussive agents alone after the clinical diagnosis before the definitive diagnosis.

The authors state that they have no Conflict of Interest (COI).

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