Effect of Palivizumab Prophylaxis on Subsequent Recurrent Wheezing in Preterm Infants

WHAT'S KNOWN ON THIS SUBJECT: Palivizumab prophylaxis prevents respiratory syncytial virus lower respiratory tract infection. An association between respiratory syncytial virus infection and subsequent recurrent wheezing has been suggested by many studies. Only a few studies conducted from Europe and North America have addressed this causal association.

WHAT THIS STUDY ADDS: In a prospective, multicenter, case-control study of 440 children with high follow-up rate of 98.4%, palivizumab prophylaxis administered to preterm Japanese infants (33–35 weeks' gestational age) in their first respiratory season reduced the incidence of subsequent recurrent wheezing up to 3 years.

abstract

BACKGROUND AND OBJECTIVES: Palivizumab effectively prevents severe respiratory syncytial virus (RSV) disease in preterm infants. Our objective was to test whether palivizumab prophylaxis given to preterm infants during the first RSV season reduces the incidence of subsequent recurrent wheezing up to 3 years of life.

METHODS: We conducted an observational prospective multicenter (52 registered hospitals in Japan) case-control study in preterm infants with a gestational age between 33 and 35 weeks followed for 3 years. During the 2007–2008 RSV season, the decision to administer palivizumab was made based on standard medical practice. In April 2008, 52 hospitals were recruited. Study participants were prospectively followed to the age of 3 years. Parents of study subjects reported the infants’ physician's assessment of recurrent wheezing, used a report card and a novel mobile phone-based reporting system by using the Internet. The primary end point was the incidence of physician-diagnosed recurrent wheezing.

RESULTS: Of 444 preterm infants enrolled, 349 received palivizumab during the first 6 months of life and 95 infants did not. Physician-diagnosed recurrent wheezing was observed in 6.4% and 18.9% of infants in the treated and untreated groups, respectively ($P < .001$). This difference remained significant after adjustment for known risk factors of recurrent wheezing ($P < .001$).

CONCLUSIONS: Palivizumab prophylaxis administered to preterm infants 33 to 35 weeks' gestational age is associated with a significantly lower incidence of recurrent wheezing during the first 3 years of life. Pediatrics 2013;132:811–818

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KEY WORDS
respiratory syncytial virus, atopic asthma, mobile phone based reporting

ABBREVIATIONS
CI—confidence interval
HR—hazard ratio
IgE—immunoglobulin E
RR—relative risk
RSV—respiratory syncytial virus
wGA—weeks’ gestational age

This trial has been registered at www.clinicaltrials.gov (identifier NCT01072552).

(Continued on last page)
Numerous investigations into the inception of bronchial asthma have revealed that lower respiratory tract infection with respiratory syncytial virus (RSV) during infancy or early childhood is associated with recurrent wheezing and asthma in later childhood.1–6 It has also been reported that the development of RSV-related lower respiratory tract infection in preterm infants is associated with an increased prevalence of serious early childhood wheezing between the ages of 2 and 3 years.7

Palivizumab is a humanized anti-RSV monoclonal antibody that binds to the RSV fusion protein, neutralizes RSV, and inhibits viral replication.8 Monthly administration of palivizumab to preterm infants has been shown to reduce the incidence of hospitalization due to RSV lower respiratory tract infection.9 Thus, it is possible that the prevention of severe RSV-related lower respiratory tract infection by using palivizumab during infancy can reduce recurrent wheezing as shown in a recent matched cohort study conducted in Europe and Canada.10

Since the clinical benefit of palivizumab in preventing hospitalization of preterm infants due to severe lower respiratory tract RSV infection has been well established, it is unethical to conduct a randomized clinical trial with a placebo control arm in this population. However, in the population of preterm infants (33–35 weeks’ gestational age [wGA]), those who do not receive palivizumab prophylaxis are found relatively frequently in the clinical setting. This prompted our study design of an observational study, in which respiratory outcomes were prospectively followed without intervention once the decision for RSV prophylaxis during the first RSV season was made. This allowed us to address the important question of the effectiveness of RSV prophylaxis upon the development of subsequent recurrent wheezing in a real world clinical setting. To improve the follow-up rate among the study population, the study used a novel mobile phone-based follow-up system utilizing a camera and QR code reader application to simplify reporting procedures.

METHODS

Study Design, and Primary and Secondary End Points

This was a prospective, multicenter, observational case-control study to compare the incidence of subsequent physician-diagnosed recurrent wheezing in the 2 groups of children. The first group consisted of preterm infants 33 to 35 wGA who had received palivizumab prophylaxis during their first RSV season. The second group comprised infants who never received palivizumab during the same RSV season. The secondary end points were measured after the first RSV season and up to 3 years of age. They were (1) the frequency of children with 3 or more episodes of expiratory wheezing and high serum immunoglobulin E (IgE) levels, and (2) the mean number of outpatient visits and hospitalizations due to respiratory-related diseases.

Study Population

A total of 52 medical centers throughout Japan, in which parents of preterm infants with 33 to 35 wGA born between July 1 and December 31, 2007, were recruited to the study. The use of palivizumab prophylaxis for preterm infants during their first RSV season was decided based on the local medical practice at each hospital and parents’ preference. Parents of all eligible preterm infants less than a year of age were recruited to the study between April and December 2008. Thus, study subjects had already either completed RSV prophylaxis or did not receive RSV prophylaxis in their first year of life, before the enrollment. Written informed consent was collected from each infants’ parents or caregivers at study enrollment.

The exclusion criteria were small for gestational age (less than —2.5 SD of reference birth weight), chronic lung disease, and history of respiratory diseases requiring mechanical ventilation regardless of pulmonary surfactant use. Infants who had received fewer than 3 doses of palivizumab during the first 6 months of life were also excluded as used in a previous study.10

Follow-up of Children

Infants enrolled in the study were prospectively followed up until their third birthday. To try and standardize medical care among their children, all parents of enrolled children were informed to visit a hospital/clinic when their children showed common cold-like symptoms such as coughing, wheezing, loss of appetite, or fever. It is common clinical practice for Japanese parents to seek hospital care for sick children younger than 3 years of age. To minimize reporting bias, we trained parents on the use of mobile phone-based reporting system by using dummy data at enrollment. The parents were given a small card on which physicians examining their child for respiratory symptoms recorded the presence or absence of expiratory wheezing and its duration. The parents were instructed to bring the card with their child and ask the attending physician to fill it out when the child visited a hospital or clinic due to respiratory symptoms. The patient was requested to visit the physician again 24 hours later to confirm if the wheezing persisted for 24 hours, and the physician described the finding on the card. After obtaining new information on wheezing, the parents took a picture of the filled-in card by using their mobile
phone camera, and sent it immediately to the research center over the Internet by using a QR code printed on the card. In addition, parents submitted monthly reports via a mobile phone-based automated answering system about the presence or absence of expiratory wheezing in their child, and the number of hospital/clinic visits and hospitalizations due to respiratory-related illness, RSV testing, or infection. The parents were reached by telephone if they failed to submit the monthly mobile phone report.

A blood examination was performed to measure serum IgE levels in the month of their third birthday.

**Respiratory Assessment**

Measures of respiratory outcome and clinical assessments were developed based on previous epidemiologic studies on the long-term effects of RSV. An episode of expiratory wheezing was defined as bronchial obstruction lasting at least 24 hours preceded by at least a 1-week nonwheezing healthy period. Recurrent wheezing was defined as the occurrence of 3 or more episodes of expiratory wheezing diagnosed by a physician in a 12-month period as previously reported. Children who met the IgE-related secondary end point (ie, occurrence of 3 or more episodes of physician-diagnosed expiratory wheezing before the third birthday and a high serum total IgE level and/or a positive serum IgE to *Dermatophagoides pteronyssinus* at the age of 3 years) were identified as a high-risk population for future development of atopic asthma. The serum IgE levels were determined by using an in vitro diagnostics kit (Thermo Fisher Scientific, Inc, Waltham, MA). The cutoff values for elevated IgE were defined as >30 IU/mL and >0.35 IU/mL for total and specific IgE serum levels, respectively, in accordance with the package inserts for these kits.

**Statistical Methods**

Target sample sizes of 300 infants for the palivizumab-treated group and 150 infants for the untreated group would provide 80% power (assuming a 10% drop-out rate) to detect a significant difference at a 5% level to compare the incidence of recurrent wheezing between the 2 groups with a 50% reduction in the palivizumab-treated cohort from a base line incidence rate of recurrent wheezing at ~14.0%. Demographics and baseline characteristics were compared between the groups by using Student’s *t* test or Wilcoxon sign-rank test for quantitative variables, and the *χ*² test or Fisher’s exact test for categorical variables. A Fisher’s exact test was used to determine statistical significance for differences in incidence rates of recurrent wheezing and atopic asthma between the 2 groups. The 95% confidence intervals (CIs) for the relative risk (RR) were also calculated.

Possible confounders for their potential association with recurrent wheezing were chosen based on significant background differences in groups on univariate analyses and clinical relevance. Gestational age, presence or absence of smokers in home, and a family history of allergy were equally weighted and were used for adjusting background risks in multivariate analyses.

A multiple logistic regression model adjusting for baseline factors as covariates was employed for the categorical outcomes. For the comparison of time to the onset of recurrent wheezing between the groups, a Kaplan-Meier test with the log-rank test and a Cox regression model using the same risk adjustments was used. Summary statistics of mean numbers of hospital/clinic visits and hospitalizations due to respiratory-related diseases were calculated for each group, and the differences between the groups were compared by using a Poisson regression model, adjusting for baseline factors as covariates.

The level of significance was set at 0.05 for all statistical tests.

**Approval**

The institutional review board at each center and the central institutional review board at Tokyo Women’s Medical University approved the study, and written informed consent was obtained from each infant’s parent or legal guardian before enrollment. Upon enrollment, the following demographics and baseline characteristics were obtained for each infant: birth weight, week of gestation at birth, gender, birth date, number of siblings, use of daycare center by the infant, smokers in the family, household pets, parental history of asthma, and family history of allergy (except for siblings).

**RESULTS**

**Participants and Follow-up**

A total of 349 infants who received at least 3 doses of palivizumab and 95 infants who did not receive palivizumab were enrolled. The number of the control infants was less than the target sample size calculated before the study because of more widespread use of palivizumab among preterm infants in Japan than expected. The enrollment was stopped at the end of December 2008 as predetermined in the study protocol despite fewer control subjects than the plan. The use of the mobile phone-based photo capture-Internet submission system and the automated answering system yielded a high follow-up rate, and 98.4% of parents and guardians of participating infants reported data throughout the study period. The study report cards were
retrieved from 440 of the 444 infants who participated in the study. All 4 missing cards belonged to children in the palivizumab-treated group. These 4 children were regarded as being lost-to-follow-up cases and were excluded from the analysis (Fig 1). The mean person-years of follow-up during the observation period and the mean age ± 1 SD of the infants at the end of follow-up were 1000 and 282 person-years, and 2.9 + 0.37 and 3.0 + 0.19 years old for the palivizumab prophylaxis and untreated groups, respectively.

A total of 333 children (260 palivizumab-treated children and 73 untreated children) with serum IgE test results constituted the population for analysis of the secondary end point, IgE levels at the age of 3 years (Fig 1).

**Demographics and Baseline Characteristics**

The mean birth weight, mean gestational age, gender, prevalence of infants born between July and September, and numbers of siblings were similar between the groups, whereas there were statistically significant differences between the groups in gestational age ($P = .0083$), smokers in home ($P = .011$), and family history of allergy ($P = .0049$) (Table 1).

**Respiratory Outcomes**

Recurrent wheezing was observed in 18 of the 95 (18.9%) infants in the untreated group, and in 22 of the 345 (6.4%) in the palivizumab treated group. This was an approximately threefold lower rate in the palivizumab treated group (RR, 0.34 [95% CI, 0.19–0.60], $P < .001$). A multivariable analysis confirmed the independence of the association ($P < .001$). A comparison of the time to event analysis of recurrent wheezing between the groups revealed an approximately fourfold relative reduction in the proportion of children with recurrent wheezing in the palivizumab-treated group (hazard ratio [HR], 0.23 [95% CI, 0.11–0.50]; $P < .001$) (Fig 2), which was also confirmed after adjusting with the aforementioned risk factors.

The mean total IgE was 156.1 and 198.2 IU/mL for the palivizumab recipient and control groups, respectively ($P = .38$), and the mean specific IgE was 12.6 and 8.8 IU/mL for the palivizumab recipient group and the control group, respectively ($P = .29$). For the secondary end point regarding the risk for future atopic asthma defined as elevated either total or specific IgE, univariate analysis revealed a non-significant trend toward reduction in the palivizumab-treated group ($P = .087$), which became statistically significant after adjusting for baseline factors (gestational age, smokers in home, and family history of allergy) ($P = .031$).

**Hospital/Clinic Visits and Hospitalizations Due to Respiratory-Related Diseases**

In the follow-up period, after the first respiratory season, children who received palivizumab prophylaxis in infancy had statistically significantly fewer subsequent outpatients visits due to respiratory disease (12.1 and 14.1 visits per person for the palivizumab recipients and the control infants, respectively; RR, 0.88 [95% CI, 0.83–0.94]; $P < .001$), but there was no difference in the number of hospitalizations due to respiratory disease (0.07 and 0.09 hospitalizations per person for the palivizumab recipients and the control infants, respectively; RR, 0.81 [95% CI, 0.51–1.29]; $P = .37$).

**DISCUSSION**

Concurring with the results of the matched cohort study conducted in Europe and North America, our study in a Japanese population employing a different study design demonstrates that prevention of severe RSV infection with palivizumab in preterm infants 33

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**FIGURE 1**
Flowchart of registration and outcome evaluation. Infants were enrolled from July 1 to December 31, 2007.
to 35 wGA during infancy decreases the incidence of recurrent wheezing in early childhood.

For the secondary outcomes, the number of outpatient visits due to respiratory disease was similarly reduced in the palivizumab recipient group. The reduction in number of outpatient visits was significant between the groups, whereas the number of hospitalizations did not reach statistical significance. In this study, the number of hospitalizations due to RSV infection and other causes were not distinguished.

The result of this Japanese study is consistent with the previous study, which strongly suggests that the reduction of the recurrent wheezing by RSV prophylaxis is universal, not specific to particular ethnic/geographic population.

The limitations of this study include the potential biases due to nonrandomized study design. In addition, the differences in demographics and baseline characteristics make interpretation of the results more complex. Although the differences in family history of asthma, birth weight, and gestational age were minimal, smokers in home and family members with a history of allergy were significantly more frequent in the untreated group. Bias in the enrollment process may have been minimized because notification of this study to investigators and parents of eligible infants was purposefully started after the end of the infant’s first RSV season, so that the decision on treatment choice was already made at enrollment. The medical expense related to the use of palivizumab for this infant population is completely reimbursed in Japan without out-of-pocket cost or with out-of-pocket cost that is reimbursed later, which minimizes bias due to access to palivizumab. The participating infants were allocated into the 2 groups based on local clinical practice without randomization. This decision was most likely to be affected by not only the physician’s risk assessment of the individual patient, but also hospital policy and past experiences as well as parents’ preferences. Reporting bias by parents also cannot be excluded. Nevertheless, the results of the multivariate analysis, which does adjust for confounding risk factors, indicate that administration of palivizumab is still a statistically significant and independent factor associated with a lower incidence of recurrent wheezing, suggesting a benefit of RSV prophylaxis beyond the direct effects on hospitalization achieved during prophylaxis itself.

In Japan, RSV prophylaxis in preterm infants between 33 and 35 wGA is generally accepted as a standard of care, as reflected in our cohort, and was the reason for substantially fewer than expected infants in the

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**TABLE 1 Demographics and Baseline Characteristics**

<table>
<thead>
<tr>
<th>Demographic and Risk Factors</th>
<th>Palivizumab-treated (n = 349)</th>
<th>Palivizumab-untreated (n = 95)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean birth wt, kg, mean ± SD</td>
<td>2.11 ± 0.34</td>
<td>2.19 ± 0.32</td>
<td>.058a</td>
</tr>
<tr>
<td>Mean gestational age, wk ± SD</td>
<td>34.2 ± 0.80</td>
<td>34.5 ± 0.65b</td>
<td>.0083c</td>
</tr>
<tr>
<td>Female gender, %</td>
<td>42.1</td>
<td>49.5</td>
<td>.20</td>
</tr>
<tr>
<td>Birthday in July, August, September, %d</td>
<td>47.0</td>
<td>50.5</td>
<td>.56</td>
</tr>
<tr>
<td>Mean number of siblings ± SD</td>
<td>0.9 ± 0.99</td>
<td>1.0 ± 0.97</td>
<td>.40</td>
</tr>
<tr>
<td>Subject in daycare, %</td>
<td>12.3</td>
<td>6.3</td>
<td>.14</td>
</tr>
<tr>
<td>Smokers in home, %</td>
<td>48.4</td>
<td>63.2a</td>
<td>.011d</td>
</tr>
<tr>
<td>Pets in home, %</td>
<td>23.2</td>
<td>22.1</td>
<td>.88</td>
</tr>
<tr>
<td>Parents’ history of asthma, %</td>
<td>17.2</td>
<td>23.2</td>
<td>.18</td>
</tr>
<tr>
<td>Family (except for siblings) history of allergy, %</td>
<td>53.0</td>
<td>69.5b</td>
<td>.0049d</td>
</tr>
</tbody>
</table>

a Student’s t test.
b P < .01 (significant differences between-group).
c χ² test.
d Fisher’s exact test.
e Birthday of the group of this study is between July and December.
f Wilcoxon rank sum test.
g P < .05.

**FIGURE 2**

Kaplan-Meier plot of time to the onset of recurrent wheezing. Percentage without recurrent wheezing shown for the treated group (n = 349) and the untreated group (n = 95). Infants’ age (month) is indicated on the x-axis. The study infants were followed-up until 3 years of age, whereas 4 infants in the treated group were lost to follow-up. Analysis of the time to onset by using a log-rank test revealed a significant reduction of recurrent wheezing in the treated group (P < .01). Cox regression analysis by using a background risk adjustment revealed also a significant difference (HR, 0.23 [95% CI, 0.11–0.50]; P < .001).
untreated group. Because an interventional study with a placebo control group was unethical, we employed a prospective observational study design without intervention. The use of palivizumab was decided based on medical practice at the participating hospitals. Subsequently, infants were followed prospectively for respiratory outcomes by the age of 3 years. Despite obvious limitations, this approach has an implication for other clinical studies among infants or other populations, where randomization is not allowed for ethical or other reasons.

Besides the aforementioned limitations, the strength of the study included the high follow-up rate (440/444 infants), which was achieved with the convenient mobile phone answering and photo submission system (Fig 3). The most important advantages of this system include (1) follow-up reporting mainly by parents especially mothers; (2) minimum involvement of physicians in reporting findings during clinic visits; and conveniently efficient data transfer directly to the research center, which seemingly attracted and motivated mothers. This method of data gathering and reporting may be applicable to other clinical trials, especially for younger populations who are very familiar with mobile phone-based operations. In addition, our results of the IgE-related secondary end point suggest that palivizumab prophylaxis may be beneficial in reducing the occurrence of atopic asthma in later childhood. Sigurs et al reported that RSV bronchiolitis in infancy is also an important risk factor for asthma and allergy in later childhood, whereas Simões et al reported that RSV prevention by palivizumab prophylaxis in nonatopic children decreased the RR of recurrent wheezing but

**FIGURE 3**
Mobile phone-based operation system. Images of the patient card, cell phone camera, and the QR code system to connect to the Internet are shown.
did not have any effect in infants with an atopic family history. In our study, children having both recurrent wheezing and high serum IgE levels at age 3 years were less common in the palivizumab treated group, which indicates the importance of further studies. Children participating in this study are currently being followed up to 6 years old in an extension of this study, and the study is expected to be completed in 2014.

CONCLUSIONS
Palivizumab prophylaxis in preterm infants 33 to 35 wGA is an effective intervention to prevent subsequent recurrent wheezing. This study further supports the benefit of administration of palivizumab to this group of preterm infants for better respiratory outcomes.

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