Prevention of Respiratory Syncytial Virus Infections: Indications for the Use of Palivizumab and Update on the Use of RSV-IGIV

ABSTRACT. The Food and Drug Administration recently approved the use of palivizumab (pal-e-viz-hu-mab), an intramuscularly administered monoclonal antibody preparation. Recommendations for its use are based on a large, randomized study demonstrating a 55% reduction in the risk of hospitalization attributable to respiratory syncytial virus (RSV) infections in high-risk pediatric patients. Infants and children with chronic lung disease (CLD), formerly designated bronchopulmonary dysplasia, as well as prematurely born infants without CLD experienced a reduced number of hospitalizations while receiving palivizumab compared with a placebo. Both palivizumab and respiratory syncytial virus immune globulin intravenous (RSV-IGIV) are available for protecting high-risk children against serious complications from RSV infections. Palivizumab is preferred for most high-risk children because of ease of administration (intramuscular), lack of interference with measles–mumps–rubella vaccine and varicella vaccine, and lack of complications associated with intravenous administration of human immune globulin products. RSV-IGIV, however, provides additional protection against other respiratory viral illnesses and may be preferred for selected high-risk children including those receiving replacement intravenous immune globulin because of underlying immune deficiency or human immunodeficiency virus infection. For premature infants about to be discharged from hospitals during the RSV season, physicians could consider administering RSV-IGIV for the first month of prophylaxis.

Most of the guidelines from the American Academy of Pediatrics for the selection of infants and children to receive RSV-prophylaxis remain unchanged. Palivizumab has been shown to provide benefit for infants who were 32 to 35 weeks of gestation at birth. RSV-IGIV is contraindicated and palivizumab is not recommended for children with cyanotic congenital heart disease. The number of patients with adverse events judged to be related to palivizumab was similar to that of the placebo group (11% vs 10%, respectively); discontinuation of injections for adverse events related to palivizumab was rare.

ABBREVIATIONS. RSV, respiratory syncytial virus; CLD, chronic lung disease; FDA, Food and Drug Administration; CHD, congenital heart disease; RSV-IGIV, respiratory syncytial virus immune globulin intravenous; AAP, American Academy of Pediatrics; ICU, intensive care unit; MMR, measles–mumps–rubella; IPV, inactivated poliovirus vaccine; OPV, oral poliovirus vaccine; IGIV, immune globulin intravenous.

The recommendations in this statement do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.


BACKGROUND

RSV-IGIV (RespiGam, Massachusetts Public Health Biologic Laboratories, and MedImmune, Inc, Gaithersburg, MD) was licensed by the FDA in January 1996 for prevention of severe RSV lower respiratory tract disease in infants and children younger than 24 months with CLD or a history of premature birth (≤35 weeks of gestation). Recommendations for the use of this product have been summarized previously by the American Academy of Pediatrics (AAP).1 Randomized, controlled clinical trials demonstrated the efficacy and safety of monthly RSV-IGIV infusions in selected infants.2,3 Although RSV-IGIV was the first agent with demonstrated efficacy for prophylaxis against RSV infections, and did provide a 41% reduction in RSV hospitalizations, several disadvantages are associated with this product. On the basis of available clinical trials, the safety and efficacy of RSV-IGIV in children with CHD has not been established. Children with cyanotic CHD who received RSV-IGIV and underwent cardiac surgery appeared to experience an increased surgical mortality rate.4 RSV-IGIV prophylaxis requires monthly intravenous infusion throughout the RSV season, and like palivizumab is costly.5 Also, a widespread shortage of RSV-IGIV during the past two winter seasons made supplies unreliable. The need for alternative approaches to the prophylaxis of RSV infection in high-risk infants is apparent.

A recent study using a RSV intramuscular monoclonal antibody, palivizumab, (Synagis, MedImmune, Inc, Gaithersburg, MD) provided an alternative approach to the prevention of RSV infections in high-risk infants. Palivizumab is a humanized monoclonal antibody directed against the F glycoprotein of RSV—a surface protein that is highly conserved among RSV isolates.6 Because the monoclonal antibody is not de-
rived from human immune globulin, it is free of potential contamination by infectious agents and can be produced readily in batch lots; thus, shortages are not anticipated. The recently completed IMpact-RSV clinical trial defines the usefulness of this product for prevention of RSV disease in high-risk infants.\(^7\) Palivizumab was approved by the FDA in June 1998 based on the results of this trial. This statement summarizes existing data on palivizumab and provides recommendations concerning its appropriate use in clinical practice. Previous policy from the AAP has described other aspects of RSV disease: epidemiologic characteristics, risk factors for serious illness, laboratory diagnosis, and treatment with ribavirin\(^8\) as well as use of RSV-IGIV.\(^1\)

**CLINICAL STUDIES**

**Clinical Efficacy of Palivizumab**

During the winter of 1996 and 1997, 1502 infants were enrolled in a multicenter, double-blind, randomized clinical trial of palivizumab (2:1 enrollment, treated vs placebo group). At 30-day intervals, starting at the onset of the RSV season, 5 intramuscular doses (15 mg/kg) of either palivizumab or a placebo were administered. Children eligible for participation in the clinical trial were younger than 6 months at the start of the RSV season. The primary endpoint was efficacy of prophylaxis in reducing the incidence of hospitalization for RSV infections. Secondary endpoints included the total number of hospital days attributable to RSV as well as other respiratory viruses, days of supplemental oxygen therapy, days of altered respiratory illness score (the respiratory illness score included work of breathing, respiratory rate, retractions, and oxygen requirements [greater than 3 days]), days of intensive care unit (ICU) management, days of mechanical ventilation use, and incidence of otitis media.

One hundred thirty-nine sites in the United States, Canada, and the United Kingdom participated in this clinical trial. Placebo and prophylaxis groups were balanced at the beginning of the study for demographics and RSV infection risk factors (ie, prematurity, neonatal CLD). Prophylaxis resulted in a 55% overall reduction in RSV-related hospitalizations (11% to 5% in placebo vs palivizumab recipients, respectively, \(P < .001\)). Small differences in rates of hospitalizations were noted between placebo and prophylaxis groups in different geographic regions. These rates were 10% prophylaxis compared with 5% placebo for the United States, 15% prophylaxis compared with 9% placebo for Canada, and 10% prophylaxis compared with 4% placebo for the United Kingdom.

The number of days of hospitalization for RSV infection per 100 children was decreased from 62 in patients receiving a placebo to 36 in those receiving palivizumab \((P < .001)\). Clinical benefit could be ascribed for additional secondary endpoints (Table 1), including decreased requirement for supplemental oxygen, a decrease in the number of days of moderate or severe lower respiratory tract illness per 100 children (illness severity score), or a reduction in the requirement for hospitalization in an ICU. No statistically significant differences were identified for the requirement of mechanical ventilation or in the incidence of otitis media.\(^7\) The mortality rate was low in both study populations. Among placebo recipients, 5 children died (1%) compared with 4 children who received palivizumab (0.4%). Hospital deaths during the study occurred in 2 of the palivizumab recipients, 1 attributed to aspiration and the other to complications of liquid ventilation in a child with RSV pneumonia.

Adverse events were not significant. Overall, the development of erythema, pain, and induration at the site of intramuscular injection resulted in adverse events in 2% of the placebo recipients and in 3% of infants receiving palivizumab.\(^7\) There were no significant differences in adverse event rates or the appearance of antibody to the monoclonal antibody.\(^9\) No data are available regarding the potential for adverse events or therapeutic efficacy in a second year of administration.

**Subgroup Analyses**

Palivizumab reduced the severity of clinical illness in all subgroups evaluated (Table 2). Premature infants without CLD had an overall 78% reduction in

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Palivizumab</th>
<th>% Reduction</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of RSV hospitalization, %</td>
<td>10.6</td>
<td>4.8</td>
<td>55</td>
<td>(&lt; .001)</td>
</tr>
<tr>
<td>RSV hospitalizations/100 children, day</td>
<td>62.4</td>
<td>36.4</td>
<td>42</td>
<td>(&lt; .001)</td>
</tr>
<tr>
<td>(O_2) requirement/100 children, day</td>
<td>50.6</td>
<td>30.3</td>
<td>40</td>
<td>(&lt; .001)</td>
</tr>
<tr>
<td>Incidence RSV ICU care, %</td>
<td>3.0</td>
<td>1.3</td>
<td>57</td>
<td>(0.026)</td>
</tr>
<tr>
<td>ICU/100 children, day</td>
<td>12.7</td>
<td>13.3</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation, %</td>
<td>2</td>
<td>7</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation, total number of days</td>
<td>1.7</td>
<td>8.4</td>
<td>—</td>
<td>(0.210)</td>
</tr>
<tr>
<td>All respiratory hospitalizations, %</td>
<td>22</td>
<td>16</td>
<td>27</td>
<td>(0.008)</td>
</tr>
<tr>
<td>Respiratory hospitalizations/100 children, day (including RSV)</td>
<td>180</td>
<td>124</td>
<td>31</td>
<td>(0.004)</td>
</tr>
<tr>
<td>Otitis media, %</td>
<td>40</td>
<td>42</td>
<td>—</td>
<td>NS</td>
</tr>
<tr>
<td>Deaths, %</td>
<td>1</td>
<td>4</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

* RSV-IVIG indicates respiratory syncytial virus immune globulin intravenous; ICU, intensive care unit.
+ Includes 2 infants who required prolonged ventilatory support.
hospitalization (8% in the placebo group vs 2% in the palivizumab group, \( P < .001 \)). Premature infants with CLD showed a 39% reduction (13% in the placebo group vs 8% in the palivizumab group, \( P = .038 \)). Although the overall number of children in the clinical trial allowed for comparisons of smaller groups, these assessments should be considered retrospective and exploratory.

In a retrospective subgroup analysis, reduction in the rate of RSV-associated hospitalizations from 10% in the placebo group to 1.8% in the palivizumab group was noted for children born between 32 and 35 weeks of gestation who did not have CLD. However, lower rates of hospitalization have been documented for children of similar ages who received no therapy.10

**Overall Considerations**

As noted earlier, palivizumab decreases risk of severe RSV disease, as does RSV-IGIV. No direct studies were done to compare relative efficacy of the two products. Palivizumab is not a human blood product and, therefore, is not associated with risks of acquisition of blood-borne pathogens, a potential risk with RSV-IGIV. Because of its ease of administration, palivizumab is favored over RSV-IGIV (1 intramuscular injection vs a 4-hour intravenous infusion). Furthermore, the availability of palivizumab is not contingent on the blood donor pool. Currently, palivizumab is only available in an intramuscular formulation; however, an intravenous formulation will likely be available in the near future.

The only rationale for such a formulation is to provide the capability of administering this product intravenously if the infant has an intravenous line in place for other reasons.

Escape mutants (ie, resistant viruses) to palivizumab have not been identified after the administration of this product; however, the administration of other monoclonal antibodies has been associated with development of such resistant mutants. Surveillance will be required to identify the risk for such events.

A critical aspect of RSV prevention in high-risk infants is the education of parents and other caregivers about the importance of reducing exposure to and transmission of RSV. Preventive measures include eliminating exposure to cigarette smoke and limiting exposure to contagious settings (eg, child care centers). Emphasis on hand-washing in all settings, including the home, especially during periods when contacts of high-risk children have respiratory infections or are at high risk for exposure to respiratory infections from siblings who are in child care or attend school, is also important.

**Clinical Selection of RSV-IGIV Over Palivizumab**

Although palivizumab provides effective protection against RSV for eligible infants, and has greater ease of administration and fewer adverse effects than RSV-IGIV, there may be certain considerations that might favor the use of RSV-IGIV. Specifically, in the RSV-IGIV trial, immunoprophylaxis decreased the overall rate of hospitalizations for non-RSV respiratory infections, whereas palivizumab did not. This may be of value in those infants younger than 6 months who are not eligible for influenza vaccination as well as for those infants and children with severe pulmonary disease for whom respiratory infections other than those caused by RSV may be medically important. Similarly, there was a statistically significant reduction in the overall frequency of otitis media, although this latter point alone is unlikely to justify use of RSV-IGIV. Palivizumab has not been tested in the treatment of children with CHD. Neither product is licensed by the FDA for use in children with CHD, and RSV-IGIV should not be administered to children with cyanotic CHD.

**Administration**

Palivizumab is administered intramuscularly in a dose of 15 mg/kg once a month during the RSV season. Palivizumab is packaged in 100-mg vials, and opened vials must be used within 6 hours. To minimize wastage, physicians should arrange for admission so that 2 or more eligible patients can receive the vaccine within the 6-hour period after opening a vial. RSV-IGIV is administered intravenously in a dose of 750 mg/kg once a month during the RSV season.

<table>
<thead>
<tr>
<th>TABLE 2. Prevention of Respiratory Syncytial Virus Infections: Indications for the Use of Palivizumab and Update on the Use of RSV-IGIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>All infants</td>
</tr>
<tr>
<td>Premature infants with CLD</td>
</tr>
<tr>
<td>Premature infants without CLD</td>
</tr>
<tr>
<td>Neonatal weight</td>
</tr>
<tr>
<td>&gt;5 kg</td>
</tr>
<tr>
<td>&lt;5 kg</td>
</tr>
<tr>
<td>Neonatal gestational age</td>
</tr>
<tr>
<td>&lt;32 wk</td>
</tr>
<tr>
<td>32–35 wk†</td>
</tr>
</tbody>
</table>

* CLD indicates chronic lung disease.
† Rates for infants (\( N = 355 \) total) born at 32 to 35 weeks of gestation, but without CLD, were 10% and 1.8% for placebo and palivizumab recipients, respectively.
Vaccination

Palivizumab does not interfere with vaccine administration. Infants and children receiving RSV-IGIV prophylaxis (750-mg/kg dose) immunization with measles–mumps–rubella (MMR) and varicella vaccines should be deferred for 9 months after the last dose. (See Table 3.37 on page 353 of the 1997 Red Book.) There are no data on the use of RSV-IGIV and the response to hepatitis B vaccine, but there is no reason to anticipate interference because RSV-IGIV does not contain antibodies to hepatitis B surface antigen. RSV-IGIV use should not alter the primary immunization schedule for diphtheria and tetanus toxoids, whole-cell or acellular pertussis, Haemophilus influenzae type b, and poliovirus vaccines (inactivated poliovirus vaccine [IPV] or oral poliovirus vaccine [OPV]). The manufacturer of RSV-IGIV has suggested that an additional dose of vaccine might be needed to assure an adequate immune response to diphtheria and tetanus toxoids, whole-cell or acellular pertussis. Haemophilus influenzae type b, and OPV (refer to the RespiGam package insert), but more information is needed before changes in current immunization recommendations can be made. Currently, the available data do not support the need for supplemental doses of routinely administered vaccines. Parenterally administered immunoglobulin preparations have little, if any, effect on the replication of OPV in the intestinal tract.

Cost-benefit Analyses

Only limited cost-benefit analysis data are available for RSV-IGIV, and no peer-reviewed data are available at this time for palivizumab. Cost-benefit analyses of RSV-IGIV did not demonstrate an overall savings in hospitalization considering the costs of therapy for all at-risk children. Although results of another study were more favorable, different methods were used.

Factors other than CLD influence the decision about use of prophylaxis, particularly in children with a gestational age of 32 to 35 weeks, including other underlying conditions that predispose to respiratory complications (eg, neurologic disease in very low birth weight infants), number of young siblings, child care center attendance, exposure to tobacco smoke in the home, anticipated cardiac surgery, and distance to and availability of hospital care for severe respiratory illness. For many infants qualifying for the approved indications, risk of rehospitalization for serious respiratory illness will be low, and the cost and logistical difficulties associated with prophylaxis may outweigh the potential benefits.

RECOMMENDATIONS

1. Palivizumab or RSV-IGIV prophylaxis should be considered for infants and children younger than 2 years of age with CLD who have required medical therapy for their CLD within 6 months before the anticipated RSV season. Palivizumab is preferred for most high-risk children because of its ease of administration, safety, and effectiveness. Patients with more severe CLD may benefit from prophylaxis for two RSV seasons, especially those who require medical therapy. Decisions regarding individual patients may need additional consultation from neonatologists, intensivists, or pulmonologists. There are limited data on the efficacy of palivizumab during the second year of age; risk of severe RSV disease exists for children with CLD who require medical therapy. Although those with less severe underlying disease may receive some benefit for the second season, immunoprophylaxis may not be necessary.

2. Infants born at 32 weeks of gestation or earlier without CLD or who do not meet the criteria in recommendation 1 also may benefit from RSV prophylaxis. In these infants, major risk factors to consider are gestational age and chronicologic age at the start of the RSV season. Infants born at 28 weeks of gestation or earlier may benefit from prophylaxis up to 12 months of age. Infants born at 29 to 32 weeks of gestation may benefit most from prophylaxis up to 6 months of age. Decisions regarding duration of prophylaxis should be individualized, according to the duration of the RSV season. Practitioners may wish to use RSV rehospitalization data from their own region to assist in the decision-making process.

3. Given the large number of patients born between 32 to 35 weeks and the cost of the drug, the use of palivizumab in this population should be reserved for those infants with additional risk factors (see “Cost-benefit Analyses” section) until more data are available.

4. Palivizumab and RSV-IGIV are not licensed by the FDA for patients with CHD. Available data indicate that RSV-IGIV is contraindicated in patients with cyanotic CHD. However, patients with CLD, who are premature, or both, who meet the criteria in recommendations 1 and 2 and who also have asymptomatic cyanotic CHD (eg, patent ductus arteriosus or ventricular septal defect) may benefit from prophylaxis.

5. Palivizumab or RSV-IGIV prophylaxis has not been evaluated in randomized trials in immunocompromised children. Although specific recommendations for immunocompromised patients cannot be made, children with severe immunodeficiencies (eg, severe combined immunodeficiency or severe acquired immunodeficiency syndrome) may benefit from prophylaxis. If these infants and children are receiving standard immune globulin intravenous (IGIV) monthly, physicians may consider substituting RSV-IGIV during the RSV season.

6. RSV prophylaxis should be initiated at the onset of the RSV season and terminated at the end of the RSV season. In most areas of the United States, the usual time for the beginning of RSV outbreaks is October to December, and termination is March to May, but regional differences occur. The onset of RSV infection occurs earlier in southern states than in northern states. Practitioners should contact their health departments and/or diagnostic virology laboratories in their geographic areas to determine the optimal time to begin administration.
7. RSV is known to be transmitted in the hospital setting\textsuperscript{17} and to cause serious disease in high-risk infants.\textsuperscript{18–20} In high-risk hospitalized infants, the major means to prevent RSV disease is strict observance of infection control practices, including the use of rapid means to identify and cohort RSV-infected infants.\textsuperscript{21} If an RSV outbreak is documented in a high-risk unit (eg, pediatric intensive care unit), primary emphasis should be placed on proper infection control practices. The need for and efficacy of prophylaxis in these situations has not been evaluated.

8. The guidelines for modification of immunizations after RSV-IGIV have not changed. Palivizumab does not interfere with the response to vaccines.

**REFERENCES**

1990–1996. Presented at RSV After 40 Years: An Anniversary Symposium; November 9–12, 1996; Charleston, SC. Abstract


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