

# PEDIATRIC PHARMACOTHERAPY

A Monthly Newsletter for Health Care Professionals from the  
Children's Medical Center at the University of Virginia

• celebrating 10 years of publication •



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Volume 10 Number 9

September 2004

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## Update on Palivizumab

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**R**espiratory syncytial virus (RSV) is one of the leading causes of severe respiratory illness in infants and young children. Premature infants, infants with chronic lung disease (CLD), and infants with congenital heart disease (CHD) are known to be at greater risk for severe RSV infection. Since its release in 1998, palivizumab, a monoclonal antibody to RSV, has been shown to reduce the incidence of severe infection in these high-risk patients.<sup>1-3</sup> This issue of *Pediatric Pharmacotherapy* will review the pharmacology of palivizumab, as well as recently published clinical trials and the revised guidelines for its use published by the American Academy of Pediatrics (AAP).

### Mechanism of Action

Palivizumab is a humanized monoclonal antibody directed to an epitope in the A antigenic site of the F protein of RSV. It is a composite of primarily human antibody sequences (95%) and murine antibody sequences (5%). Palivizumab provides both neutralizing and fusion-inhibitory activity against RSV, resulting in inhibition of RSV replication. Although resistant RSV strains have been isolated in laboratory experiments, no resistant clinical isolates have been identified at this time.<sup>4,5</sup>

### Clinical Trials

The efficacy of palivizumab has been demonstrated in two large randomized, double-blind, placebo-controlled trials.<sup>6,7</sup> The first of these, the Impact-RSV trial, enrolled 1,502 infants.<sup>6</sup> Criteria for enrollment included gestational age less than 35 weeks and/or the presence of CLD. Patients were randomized in a 2:1 manner (palivizumab: placebo). Those in the treatment group received palivizumab 15 mg/kg intramuscularly (IM) monthly for 5 months. The use of palivizumab resulted in a 55% overall

reduction in hospitalization for RSV infection (the primary endpoint). The hospitalization rate was 4.8% in the treatment group versus 10.6% in the controls. The total days of hospitalization was also significantly lower in the treatment group (36.4 days per 100 children) compared to the controls (62.6 days per 100 children). There were also decreases in the need for supplemental oxygen, the illness severity score, and the need for intensive care in the treatment group. No difference was noted in the need for mechanical ventilation. Adverse effects were similar in both groups.

In 2003, Feltes and colleagues published a randomized, double-blind, placebo-controlled trial of palivizumab in 1,287 infants and young children with hemodynamically significant CHD.<sup>7</sup> Patients with CHD are known to be at risk for severe complications from RSV, but treatment with RSV immune globulin (RSV-IG), an earlier product for RSV prophylaxis, resulted in an unanticipated increase in adverse effects at the time of cardiac surgery.<sup>8</sup>

The CHD trial used the same drug administration strategy as the Impact-RSV study. Patients were randomized in a 1:1 manner and were stratified into cyanotic and noncyanotic groups. Overall, palivizumab-treated patients had a 45% decrease in hospitalization for RSV infection (5.3% versus 9.7% in the controls). There was a 58% reduction in hospitalization in the acyanotic patients and a 29% reduction in the cyanotic group. In addition, there was a 56% reduction in total days of RSV-related hospitalization and a 73% reduction in days of supplemental oxygen. Number of intensive care admissions and number of patients requiring mechanical ventilation were not significantly different between the groups. There were no serious adverse reactions.<sup>7</sup>

In addition to these two controlled trials, a number of institutions have published their results after implementation of palivizumab prophylaxis.<sup>9-14</sup> In a 2003 supplement to *The Pediatric Infectious Disease Journal*, Romero reviewed the results of two prospective multicenter registries as well as the results of two years of data from the Palivizumab Outcomes Registry.<sup>9</sup> The rate of hospitalization for RSV infection in treated patients was 1.5 to 2.9%, compared to an estimated rate of 3.6 to 13.4% in historical controls.

A study group from Spain found a rate of RSV-related hospitalization in 1,919 palivizumab-treated patients of 3.95%, compared to a rate of 12.25% in a matched cohort of 1,583 infants who did not receive prophylaxis.<sup>11</sup> In a recent study from France, the rate of RSV-hospitalization was 6.1% among 376 palivizumab-treated infants born at less than 33 weeks gestation, compared to a rate of 7.2% in 2,256 untreated controls.<sup>14</sup> The rate of hospitalization varies a great deal among these epidemiologic studies, as criteria for prophylaxis and hospitalization differs among institutions.

#### Recommendations for Use

Based on the efficacy and safety demonstrated in these clinical trials, in December 2003, AAP released a new policy statement revising their recommendations on the use of palivizumab. The updated policy recommends that RSV prophylaxis be considered in:

- infants and children younger than 2 years of age who have required medical therapy for CLD within the 6 months prior to the start of RSV season; patients with severe CLD may benefit from prophylaxis with palivizumab through 2 RSV seasons
- infants born at or prior to 32 weeks gestation
- infants born between 32 and 35 weeks gestation with known risk factors, such as birth within 6 months of RSV season, child care attendance, school-age siblings, exposure to environmental pollutants, airway abnormalities, or severe neuromuscular disease
- infants and children younger than 2 years of age with hemodynamically significant CHD, particularly patients with pulmonary hypertension or cyanotic heart disease, and those who require medication for congestive heart failure.<sup>1</sup>

#### Pharmacokinetics

In a study of 62 children 2 years of age and younger who were given monthly palivizumab, the mean elimination half-life was 20 days. In the 22 subjects who received doses of 15 mg/kg, the average trough serum drug concentration at the end of the first month was 60.6 mcg/ml (range 21.4-149.9 mcg/ml). This exceeds the level of 40 mcg/ml that has been associated with a reduction in RSV replication in animal models. Trough concentrations rose with the second dose to an average of 70.7 mcg/ml (range 20.2-112.9 mcg/ml) and remained above 40 mcg/ml with all subsequent doses (range 46-96 mcg/ml).<sup>15</sup> Similar serum palivizumab concentrations were found in the Impact-RSV study and in studies of infants with CHD.<sup>4,6</sup>

Cardiopulmonary bypass has been shown to significantly reduce palivizumab concentrations. In a study of 139 children under 2 years of age with CHD, mean serum palivizumab concentrations declined from a baseline of 98±52 mcg/ml before bypass to 41±33 mcg/ml after bypass, a 58% reduction.<sup>4,5</sup>

#### Adverse Effects

Administration of palivizumab is generally well tolerated. The most commonly reported adverse effects during clinical trials included upper respiratory tract infection (50.6% of treated patients versus 47.4% in the placebo group), otitis media (36.4% versus 34.6%), fever (27.1% versus 25.2%), rhinitis (26.8% versus 24.6%), rash, diarrhea, cough, wheezing, vomiting and gastroenteritis (1 to 5% in both groups).<sup>4,5,16,17</sup>

In trials of infants with CHD, cyanosis was reported in 9.1% of palivizumab recipients versus 6.9% of infants given placebo. Arrhythmias occurred in 3.1% of the palivizumab patients compared to 1.7% of controls. There have been rare reports of hypersensitivity reactions. The incidence of anaphylaxis is estimated at less than 1 case per 100,000 patients treated.<sup>4,5</sup>

No fatalities have been attributed to palivizumab administration during clinical trials or post-marketing surveillance. There has been concern that the administration of palivizumab may worsen underlying conditions in infants with CLD or CHD, but this has not been found to occur. In an analysis of 133 deaths reported to the Food and Drug Administration in infants receiving palivizumab, mortality was attributed to the patients' congenital anomalies or prematurity.<sup>18</sup> No causal relationship with palivizumab was established.

### Availability and Dosing

Palivizumab (Synagis<sup>®</sup>, MedImmune) is available in 50 and 100 mg preservative-free single-use vials. The recommended dose of 15 mg/kg should be administered IM into the anterolateral aspect of the thigh. Volumes greater than 1 ml should be divided and given in two sites. The manufacturer recommends that the vial contents be used within 6 hours of reconstitution.<sup>4,5</sup>

Palivizumab should be administered on a monthly basis throughout the RSV season, typically the 5-month period from November through March. The timing of administration should be tailored to the usual pattern of RSV infection in the patient's community.<sup>4,5</sup> Doses may be administered in the clinic setting or in the home by a health care provider. Two recent papers suggest a higher rate of compliance when administration occurs in the home.<sup>19,20</sup>

Because of the reduction in serum palivizumab concentration associated with cardiopulmonary bypass, infants with CHD who require cardiopulmonary bypass during surgery should receive a dose of palivizumab as soon as possible after the procedure to ensure adequate serum concentrations (> 40 mcg/ml). Dosing may then be resumed on a monthly schedule.<sup>4,5</sup>

### Cost

The average wholesale price (AWP) is \$780.15 for the 50 mg Synagis<sup>®</sup> vial and \$1,416.48 for the 100 mg vial.<sup>21</sup> Several cost-benefit analyses have been performed to assess the impact of palivizumab prophylaxis.<sup>22-26</sup> The results of these analyses have been mixed. In 2002, Kamal-Bahl and colleagues conducted an assessment of 12 papers describing an economic evaluation of palivizumab and/or RSV-IG.<sup>23</sup> The authors found a wide range of results, from significant cost savings with prophylaxis in some institutions to an increased overall cost in others. Differences in patient selection, methods for analysis, and tabulation of cost per hospitalization make comparisons of these studies difficult. Determining the cost-benefit of RSV prophylaxis may be best done at the institutional level, to account for the number of high-risk patients typically seen, the length of the RSV season in that geographic area, and the availability of clinic and home health care support.

### Summary

Palivizumab has been shown to be a useful tool in the prevention of RSV infections in premature infants, especially those with CLD. A recent study has also demonstrated a significant

reduction in hospitalization due to RSV infection when used in infants with CHD. While economic analyses have generally failed to show a cost benefit from widespread use, limiting the use of palivizumab to these high-risk populations appears to provide significant benefit.

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## **Pharmacology Literature Review**

### **Atomoxetine Review**

This extensive review is recommended reading for all health care providers using atomoxetine in the treatment of patients with attention deficit/hyperactivity disorder. The authors provide very useful summary tables of the studies of atomoxetine published to date, dividing them into studies in children and adolescents and studies in adults, as well as post-hoc and pooled analyses. Christman AK, Fermo JD, Markowitz JS. Atomoxetine, a novel treatment for attention-deficit-hyperactivity disorder.

**Pharmacotherapy 2004;24:1020-36.**

### **Omalizumab Review**

Omalizumab is a unique drug for the management of allergic asthma. It binds immunoglobulin E (IgE), attenuating both the early and late allergic response. This review of omalizumab describes the clinical trials conducted to date, as well as basic pharmacokinetic, dosing, and adverse effect information. The author also addresses the issues of compliance and cost with this new

therapy. Davis LA. Omalizumab: a novel therapy for allergic asthma. **Ann Pharmacother 2004;38:1236-42.**

### **Pharmacoepidemiologic Study Designs**

This article is the first in a two-part series reviewing the design of pharmacoepidemiologic studies, including cohort, case-control, and case-crossover studies. The authors describe different methodologies used to study drug use in large populations, and address both the benefits and limitations of this type of observational research. Etminan M, Samii A. Pharmacoepidemiology I: a review of pharmacoepidemiologic study designs. **Pharmacotherapy 2004;24:964-9.**

### **Unintentional infusion of Golytely®**

The author of this case describes the accidental infusion of polyethylene glycol/electrolyte solution (Golytely®). A 4 year old child was admitted to their institution after ingestion of approximately 24 tablets of 6-mercaptopurine. Golytely® was one of the therapies initiated, to be given through a nasogastric tube, to promote evacuation of the gastrointestinal tract. Instead, the Golytely® solution was inadvertently given intravenously. At the time the error was noted, 391 ml had been infused. The patient showed no signs of acidosis, renal dysfunction, or ethylene glycol toxicity. The author recommends that specific protocols be designed for the use of Golytely® in toxicologic cases to avoid future errors. Rivera W. Unintentional intravenous infusion of Golytely® in a 4-year-old girl. **Ann Pharmacother 2004;38:1183-5.**

### **Formulary Update**

The Pharmacy and Therapeutics Committee did not meet during August.

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