Abstracts from the Literature

PALIVIZUMAB PROPHYLAXIS REDUCES HOSPITALIZATION DUE TO RESPIRATORY SYNCYTIAL VIRUS IN YOUNG CHILDREN WITH HEMODYNAMICALLY SIGNIFICANT CONGENITAL HEART DISEASE. Feltes TF, Cabalka AK, Meissner HC, Piazza FM, Carlin DA, et al. J Pediatr 2003;143:532-40.

Background: Respiratory syncytial virus (RSV) affects more than 120,000 infants in the United States annually.[1] RSV infection begins with nonspecific symptoms for several days, such as, rhinorrhea, nasal congestion and fever. Then, lower respiratory involvement occurs quickly with abrupt changes in breathing patterns. Patients infected with RSV can experience tachypnea, increased work of breathing, hyperinflation of the chest wall, retractions on inspiration, fine crackles and wheezes on auscultation. Most cases of RSV are mild and only require supportive treatment in the home. There are several groups of infants that have high morbidity and mortality rates associated with RSV infection. These include infants with prematurity, chronic lung disease (CLD), congenital heart disease (CHD) and immune deficiency. The obstructive presentation of lung function is treated largely supportive and often includes the use of bronchodilators (i.e. albuterol). Initial studies evaluated the use of RSV-IG for prophylaxis of patients with CHD. This treatment has largely been replaced by palivizumab secondary to the convenience of treatment and cost. In the IMPACT trial, palivizumab was studied for use in children with CHD if their heart disease was hemodynamically stable and they had other risk factors including prematurity or CLD.[2]

Purpose: The purpose of this study is to address the safety, tolerance and efficacy of palivizumab in infants and young children with hemodynamically significant CHD.

Study design, setting and participants: This study is a multi-center, randomized, double-blind, placebo controlled trial in children with CHD conducted during 4 consecutive RSV seasons (1998-2002). Each child only participated in the study for 1 year. Children were eligible for the study if they were ≤ 24 months old at time of randomization, had documented hemodynamically significant CHD and if they possessed unoperated or partially corrected CHD. Children were excluded if they had unstable cardiac/respiratory status; were hospitalized (unless discharged planned within 21 hours); anticipated cardiac surgery within 2 weeks of randomization; required mechanical ventilation, ECMO and/or CPAP; had non-cardiac anomalies and/or end-organ dysfunction resulting in possible death; known HIV infection; acute RSV or other respiratory infection; previous receipt of palivizumab; receipt of investigational agents within 3 months or current participation in other investigation protocols within 3 months.

Methods: Patients were randomized to receive 15 mg/kg palivizumab or an equal volume of placebo by intramuscular injection every 30 days for total of 5 doses. Children were followed for 150 days from receiving their first injection (30 days after last injection). All hospitalizations were identified and RSV antigen testing of respiratory secretions was performed. Serum was collected before the first, second and fifth injections and analyzed for neutralizing antibody titers by plaque reduction neutralization test. If bypass was necessary, serum concentrations were obtained before bypass and following bypass to assess the effect of bypass surgery on serum concentrations.

Results: A total of 1287 patients were randomized, 639 in the palivizumab group and 648 placebo group. In the palivizumab group 95% (610/639) and 95.5% (618/648) in the placebo group completed the study (total finished = 1228). Monthly palivizumab injections were associated with a 45% relative reduction in RSV hospitalization. Twelve patients (9 – placebo and 3 – palivizumab) had nosocomial RSV hospitalizations. Five patients (3 – placebo and 2 – palivizumab) had more than 1 RSV hospitalization. Cochran-Mantel-Haenszel analysis was used to measure RSV hospitalizations between the cyanotic vs. acyanotic groups and RSV hospitalization across demographic differences. This analysis showed the results were highly significant indicating a benefit across the subgroups. Serum concentrations were only detected in 7.9% of the palivizumab group prior to the second dose. Also, serum concentrations measured after bypass surgery was 58% lower than baseline measured prior

to bypass surgery. As a result of safety and tolerability, no children discontinued the study drug for adverse events and no deaths were associated with study drug. There were 11 deaths (6-palivizumab, 5-placebo) that were surgery related, and there were 6 deaths (2-palivizumab, 4-placebo) that were related to severe RSV infections. Adverse drug reactions occurring in the palivizumab group attained absolute incidence > 1% higher than the placebo group included fever, reaction at the injection site, upper respiratory infections, conjunctivitis, arrhythmias and cyanosis.

Conclusions: This trial demonstrates the benefit of palivizumab use in hemodynamically significant CHD, a high-risk population for RSV infection. In the cyanotic group, RSV hospitalizations were reduced by 29% (7.9% placebo, 5.6% palivizumab). In the acyanotic group, RSV hospitalizations were reduced by 58% (11.8% placebo, 5.0 % palivizumab). Overall, palivizumab was associated with a 56% reduction in hospital days because of RSV infection. And, of the infants requiring hospitalization secondary to RSV infection, the palivizumab children had less severe cases measured by fewer days in the ICU, fewer days requiring oxygen therapy, and fewer days requiring mechanical ventilation. Patients that underwent cardiopulmonary by-pass surgery had palivizumab serum concentrations after bypass surgery that were 58% lower than levels measured prior to bypass surgery suggesting a need to give an additional dose after surgery to maintain effective immunity. Serum concentrations of the palivizumab group prior to the second dose were only detected in 7.9% of the patients proving a requirement of multiple doses to achieve adequate immunity. This studied concluded that palivizumab was safe and efficacious in hemodynamically significant CHD.

Discussion: Palivizumab is indicated for the prevention of lower respiratory tract disease caused by RSV in high-risk children. The results in this trial, a 45% relative reduction in hospitalization, were similar to the results seen in the IMPACT trial, a 55% relative reduction in hospitalization, which excluded patients with significant hemodynamic CHD.[2] The use of RSV-IG for RSV prophylaxis was evaluated CHD patients.[3] At the time, 1998, palivizumab was not available and RSV-IG was the only drug available for use against RSV. Conclusions from that study suggested that there was not a clinically significant difference between the patients that received RSV-IG and those that did not. The study also concluded that patients with significant hemodynamic CHD did not experience less RSV hospitalization but it was effective in preventing RSV hospitalizations in infants < 6 months.[3] The adverse events in the CHD patients receiving palivizumab were similar to the patients in the placebo group. Data obtained during this study demonstrates a requirement of additional palivizumab dosing if the child undergoes cardiopulmonary bypass as a result from cardiac surgery. The literature supports that palivuzumab use in RSV prophylaxis significantly reduces hospitalization and severity of illness in the premature infant as well as the infants with CHD and CLD.

REFERENCES

1. Institute of Medicine Committee on Issues and Priorities for New Vaccine Development. Prospects for immunizing against respiratory syncytial virus. In: *New Vaccine Development, Establishing Priorities.* Washington, DC: National Academy of Sciences Press; 1988; 1: 397-409.
2. IM-pact RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization form respiratory syncytial virus infection in high-risk infants. Pediatrics 1998;102: 531-7.
3. Simoes EA, Sondheimer HM, Top FH, Meissner HC, Welliver RC, Kramer AA, Groothuis JR. Respiratory syncytial virus immune globulin for prophylaxis against respiratory syncytial virus disease in infants and children with congenital heart disease. The Cardiac Study Group. J Pediatrics 1998; 133(4):492-9.
4. American Academy of Pediatrics. Respiratory Syncytial Virus. In: Pickering LK, editor. 2003 Red Book: Report of the Committee on Infectious Diseases. 26th ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2003. P. 523-8.

Emily Deihl, PharmD
Pharmacotherapy Resident
The University of Tennessee Center for the Health Science
LeBonheur Children's Medical Center