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ORIGINAL ARTICLE

Palivizumab Use in Subjects with Congenital Heart Disease

Results from the 2000–2004 Palivizumab Outcomes Registry

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Abstract The Palivizumab Outcomes Registry prospectively collected data on 19,548 subjects who received respiratory syncytial virus (RSV) prophylaxis with palivizumab during the 2000–2004 RSV seasons. We evaluated the characteristics of enrolled registry subjects with congenital heart disease (CHD) over the four RSV seasons and examined additional information on these subjects collected in the 2002–2004 seasons. The percentage of registry subjects with CHD increased from 4.8% (102/2116) in the first season to 11.4% (688/6050) in the last season. Across all four seasons, 1500 subjects with CHD were enrolled, 71% of whom had acyanotic CHD. The proportion with cyanotic CHD increased from 19.6% (20/102) in the 2000–2001 season to 37.5% (258/688) in the 2003–2004 season, while the proportion of all CHD in the registry more than doubled during this time. The cumulative RSV hospitalization rate was 1.9% among patients with CHD who received prophylaxis. Among subjects with cyanotic and acyanotic CHD, hospitalization rates were 2.6% and 1.6%, respectively. Prospective data collected in the Palivizumab Outcomes Registry provide the largest published dataset available on infants with CHD receiving palivizumab and show low hospitalization rates and use consistent with prelicensure clinical trial data and revised American Academy of Pediatrics guidelines.

Keywords Prematurity · Hospitalization · Respiratory syncytial virus

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Introduction

In the United States, respiratory syncytial virus (RSV) bronchiolitis is the leading cause of hospitalization in infants younger than 1 year [10]. Infants with cyanotic or complicated congenital heart disease (CHD) are among those at increased risk of severe or fatal RSV infection [4]. Among children younger than 5 years, CHD was the most frequent underlying condition listed for bronchiolitis-associated discharges [17]. Infants or children with CHD who are hospitalized for RSV infection have a significantly more complicated clinical course (e.g., need for assisted ventilation or longer duration of oxygen supplementation) than those without CHD [11, 12, 14]. In addition, RSV infection in patients with CHD can increase postoperative complications after cardiovascular surgery [1, 9]. Moreover, some studies have shown an increased risk of RSV-related mortality in patients with CHD [11, 14].

The first licensed product for the prevention of severe RSV infection in children with CHD (excluding cyanotic CHD) was RSV immune globulin (RSV-IGIV; RespiGam®; Massachusetts Public Health and Biologic Laboratory and MedImmune, Gaithersburg, MD; no longer manufactured). Prophylaxis with RSV-IGIV was recommended by the

American Academy of Pediatrics (AAP) for infants with asymptomatic acyanotic CHD who were premature, had chronic lung disease (CLD), or both [2]. In 2003, the AAP revised their guidelines to recommend RSV prophylaxis with monthly injections of palivizumab (Synagis®; MedImmune, Gaithersburg, MD), a humanized murine monoclonal anti-F glycoprotein antibody preparation directed against RSV, for children who are 24 months or younger with hemodynamically significant cyanotic or acyanotic CHD [3]. This recommendation, also outlined in the revised 2006 AAP guidelines [4], was based on a multicenter, randomized, double-blind, placebo-controlled trial for 1287 children with hemodynamically significant CHD, which demonstrated a 45% reduction in RSV hospitalizations ($p = 0.003$) and a 73% reduction in total RSV hospital days with increased supplemental oxygen per 100 children ($p = 0.014$) for children given prophylaxis with palivizumab compared with placebo [6]. Although this trial was not powered to analyze differences among subgroups, hospitalizations were reduced by 29% in those with cyanotic CHD ($p = 0.285$) [6]. Finally, the proportion of children with adverse events was similar between treatment groups, with the incidence of serious adverse events significantly lower in the palivizumab group than in the placebo group ($p = 0.005$) [6].

To assess how palivizumab has been used among infants and children with CHD in the community, we examined data from the Palivizumab Outcomes Registry. This prospective multicenter data-collection effort tracked the characteristics of 19,548 US infants and children receiving prophylaxis with palivizumab during four consecutive RSV seasons from 2000–2004; these data have been published previously [5, 15, 16]. Here, we describe the subset of subjects with CHD enrolled in the registry over the 4 years of data collection.

Methods

Complete details of the Palivizumab Outcomes Registry have been described elsewhere [5, 15, 16]. Concisely, the registry was conducted from 2000 to 2004 at 256 unique sites across the United States. Subjects were required to have informed consent provided by a parent or guardian and received at least 1 dose of palivizumab at a participating site to be included in the registry; there were no specific exclusion criteria [5, 15].

In all four seasons, subject demographics, medical history, and environmental history were documented. Hospitalizations for a virologically confirmed RSV infection were captured; however, testing was based on investigator discretion. The Cochran-Armitage trend test was used to compare proportions of RSV hospitalizations across the four RSV seasons. No adjustment of the alpha level for subgroup analysis was performed because this was an exploratory post hoc analysis. Compliance with palivizumab injections was determined by comparing the actual number of injections received with the expected number of injections based on the month that the first injection was administered [15]. For example, patients who received their first injection in February would be expected to receive only two injections through March, whereas those who received their first injection in November were expected to receive five injections; any patient who received more than five injections was considered compliant.

Additional demographic data were collected for the 2002–2003 and 2003–2004 seasons to obtain further information about subjects with CHD. Health care practitioners were asked if the patient had hemodynamically significant heart disease at the time of enrollment and to classify the primary and secondary CHD diagnoses by selecting from a list of 18 diagnoses or specifying a diagnosis of "other." The diagnosis of hemodynamically significant heart disease was a separate question that was independent from the primary and secondary CHD diagnoses. Additional information collected related to the care of subjects with CHD included the current status of the cardiac defect in terms of surgical procedures, the type of physician responsible for primary care (e.g., pediatric cardiologist, pediatrician), the type of physician who recommended palivizumab, and where the subjects received palivizumab injections (e.g., neonatal intensive care unit, clinic/office, home).

Results

CHD Subject Characteristics: Entire Cohort

A total of 1500 subjects with CHD were enrolled over the four-season period, accounting for 7.7% of the entire registry cohort of 19,548. The percentage of registry subjects with CHD increased each season, representing 4.8% (102/2116), 5.7% (291/5091), 6.7% (419/6291), and 11.4% (688/6050) of subjects across the four RSV seasons. Thus, the proportion of subjects with CHD more than doubled from the 2000–2001 season to the 2003–2004 season. The demographic, clinical, and environmental characteristics of subjects with CHD for each of the four seasons are summarized in Table 1. Overall, 47.0% of subjects with CHD were born after 35 weeks' gestation. Among all subjects with CHD, the majority had acyanotic heart disease (71%). However, the proportion of subjects with cyanotic heart disease was higher in the fourth season compared with the first three seasons. The percentage of subjects with CHD with the comorbid

Table 1 Demographics and clinical characteristics of subjects with CHD who received palivizumab by RSV season

Characteristic	No. (%) of subjects with CHD				
	2000–2001 (n = 102)	2001–2002 (n = 291)	2002–2003 (n = 419)	2003–2004 (n = 688)	Total (n = 1500)
Type of CHD					
Acyanotic	77 (75.5)	222 (76.3)	338 (80.7)	430 (62.5)	1067 (71.1)
Cyanotic	20 (19.6)	69 (23.7)	81 (19.3)	258 (37.5)	428 (28.5)
Gestational age, weeks					
<32	39 (38.2)	102 (35.1)	152 (36.3)	175 (25.4)	468 (31.2)
32–35	22 (21.6)	62 (21.3)	108 (25.8)	135 (19.6)	327 (21.8)
>35	41 (40.2)	127 (43.6)	159 (37.9)	378 (54.9)	705 (47.0)
Chronologic age at first dose, months					
0–3	21 (20.6)	70 (24.1)	80 (19.1)	162 (23.5)	333 (22.2)
3–6	27 (26.5)	61 (21.0)	119 (28.4)	167 (24.3)	374 (24.9)
6–12	28 (27.5)	82 (28.2)	113 (27.0)	172 (25.0)	395 (26.3)
>12	26 (25.5)	78 (26.8)	107 (25.5)	187 (27.2)	398 (26.5)
Males	58 (56.9)	154 (52.9)	209 (49.9)	352 (51.2)	773 (51.5)
Birth weight <2500 g	66 (64.7)	161 (55.3)	261 (62.3)	319 (46.4)	807 (53.8)
Race/ethnicity					
White	67 (65.7)	175 (60.1)	241 (57.5)	431 (62.6)	914 (60.9)
Black	16 (15.7)	50 (17.2)	58 (13.8)	90 (13.1)	214 (14.3)
Hispanic	13 (12.7)	34 (11.7)	74 (17.7)	107 (15.6)	228 (15.2)
Of multiple birth	15 (14.7)	51 (17.5)	74 (17.7)	108 (15.7)	248 (16.5)
NICU graduate	84 (82.4)	243 (83.5)	354 (84.5)	552 (80.2)	1233 (82.2)
Received palivizumab in prior season	27 (26.5)	78 (26.8)	131 (31.3)	209 (30.4)	445 (29.7)
Medical history					
CLD/BPD	39 (38.2)	115 (39.5)	137 (32.7)	157 (22.8)	448 (29.9)
Cystic fibrosis	2 (2.0)	2 (0.7)	0 (0.0)	1 (0.1)	5 (0.3)
Environmental history					
No. of adults in household					
1	5 (4.9)	27 (9.3)	23 (5.5)	44 (6.4)	99 (6.6)
2	84 (82.4)	219 (75.3)	322 (76.8)	500 (72.7)	1125 (75.0)
>2	13 (12.7)	45 (15.5)	73 (17.4)	144 (20.9)	275 (18.3)
No. of children in household					
1	36 (35.3)	101 (34.7)	149 (35.6)	244 (35.5)	530 (35.3)
2	28 (27.5)	93 (32.0)	139 (33.2)	205 (29.8)	465 (31.0)
>2	38 (37.3)	97 (33.3)	129 (30.8)	238 (34.6)	502 (33.5)
Either subject or other children enrolled in child care	24 (23.5)	152 (52.2)	199 (47.5)	340 (49.4)	715 (47.7)
Subject currently exposed to tobacco smoke, n (%)	15 (14.7)	48 (16.5)	83 (19.8)	106 (15.4)	252 (16.8)

BPD = bronchopulmonary dysplasia; CHD = congenital heart disease; CLD = chronic lung disease; NICU = neonatal intensive care unit; RSV = respiratory syncytial virus

Note that percentages were calculated based on all subjects enrolled in each season; data missing or unknown for an individual item ranged from <1% to 4.9%

condition of chronic lung disease (CLD)/bronchopulmonary dysplasia (BPD) was lower in the fourth season compared with the first three seasons.

At the time of their first injection, 47.1% of the subjects with CHD were younger than 6 months. Additionally, 29.7% of all subjects with CHD had received at least one dose of prophylaxis with palivizumab in a prior season. Compliance with the injection schedule increased each season, from 72.0% in the first season to 85.3% in the fourth season. Across the four seasons, 83.4% of subjects with CHD were compliant with the injection regimen.

Diagnosis and Care of Subjects with CHD: 2002–2003 and 2003–2004 Seasons

Detailed follow-up information on diagnosis and care was provided for the majority [99% (413/419)] of subjects with CHD enrolled in the 2002–2003 season and all of those enrolled in the 2003–2004 season (Table 2). The percentage of subjects with CHD with hemodynamically significant disease increased from 32.7% in 2002–2003 to 50.9% in 2003–2004. In both seasons, the most common primary diagnoses were patent ductus arteriosus, ventricular septal defect, and atrial septal defect. From the 2002–2003 to the 2003–2004 season, there were decreases in the percentages of patients who had their cardiac defect fully corrected with no residual effect and who had a defect that remained uncorrected with no surgery planned.

Pediatricians were the primary provider of medical care for the majority of subjects (89.5–93.0%) and most often recommended prophylaxis with palivizumab (61.5–73.4% of subjects). A pediatric cardiologist was the primary care provider for 4.4% and 7.4% of subjects with CHD and recommended prophylaxis for 9.9% and 13.2% of these subjects in the 2002–2003 and 2003–2004 seasons, respectively. The percentage of subjects who received their injections in the pediatrician's office increased from 29.8% in 2002–2003 to 50.9% in 2003–2004.

Table 2 Diagnosis and care of subjects with CHD from the 2002–2003 and 2003–2004 RSV seasons

Diagnosis	2002–2003 (n = 413)	2003–2004 (n = 688)
Hemodynamically significant heart disease, n (%)[a]	135 (32.7)	350 (50.9)
Primary diagnosis		
Patent ductus arteriosus	97 (23.5)	140 (20.3)
Ventricular septal defect	74 (17.9)	110 (16.0)
Atrial septal defect	58 (14.0)	68 (9.9)
Single ventricle (including hypoplastic left or right ventricle)	17 (4.1)	50 (7.3)
Atrioventricular canal defect (endocardial cushion defect)	17 (4.1)	38 (5.5)
Tetralogy of Fallot	16 (3.9)	47 (6.8)
Pulmonary stenosis	14 (3.4)	31 (4.5)
Coarctation of the aorta	12 (2.9)	23 (3.3)
Transposition of the great arteries	12 (2.9)	16 (2.3)
Aortic stenosis	5 (1.2)	9 (1.3)
Pulmonic atresia with ventricular septal defect	4 (1.0)	12 (1.7)
Tricuspid atresia	3 (0.7)	11 (1.6)
Pulmonary atresia with the intact septum	1 (0.2)	4 (0.6)
Double-outlet right ventricular with transposed great arteries	1 (0.2)	9 (1.3)
Ebstein's anomaly	0	5 (0.7)
Heart murmur[b]	—	22 (3.2)
Peripheral pulmonic stenosis[b]	—	8 (1.2)
Truncus arteriosus[b]	—	7 (1.0)
Other	82 (19.9)	78 (11.3)
Current status of cardiac defect, n (%)		
Uncorrected, surgery planned for future	51 (12.3)	92 (13.4)
Uncorrected, no surgery planned	129 (31.2)	131 (19.0)
Partially corrected	53 (12.8)	154 (22.4)
Fully corrected with residual effect	31 (7.5)	53 (7.7)
Fully corrected with no residual effect	112 (27.1)	112 (16.3)
Resolved without surgery[b]	—	57 (8.3)
Unknown[b]	—	79 (11.5)
Other	37 (9.0)	10 (1.5)

CHD = congenital heart disease; RSV = respiratory syncytial virus

[a] Diagnosis of hemodynamically significant heart disease was at the health care practitioner's discretion and independent from the primary diagnosis

[b] Added in 2003–2004 season; data not available for 2002–2003 season

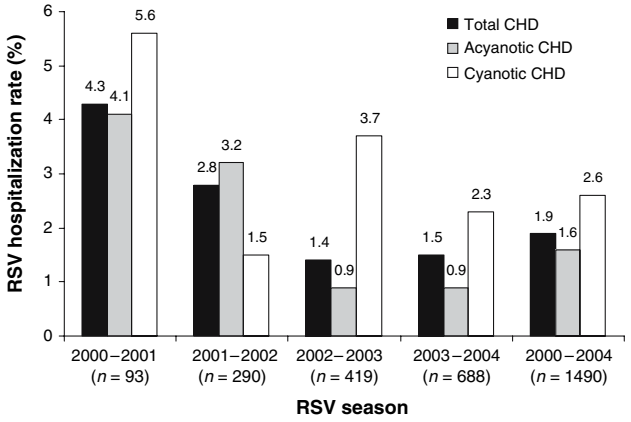

Fig. 1 Hospitalization rates among registry subjects with CHD, acyanotic CHD, and cyanotic CHD for each of the four RSV seasons and in total

Confirmed RSV Hospitalizations

Across all four seasons of the registry, follow-up information that included hospitalization data was reported for 1490 of the subjects with CHD. Overall, 1.9% of subjects with CHD prophylactically treated with palivizumab had a laboratory-confirmed RSV hospitalization (Fig. 1). This hospitalization rate was significantly higher than the rate of hospitalization among registry subjects without CHD (1.9% vs 1.2%; $p = 0.03$ based on univariate logistic regression analysis). The percentages of subjects with acyanotic and cyanotic heart disease hospitalized over the four seasons were 1.6% and 2.6%, respectively. As shown in Fig. 1, the subjects with cyanotic CHD had greater hospitalization rates than those with acyanotic CHD in three of four seasons. A decreasing trend in the proportion of RSV hospitalizations was observed across the four RSV seasons from 2002 to 2004 for all subjects with CHD ($p = 0.0215$) and subjects with acyanotic CHD ($p = 0.0046$).

Discussion

The Palivizumab Outcomes Registry provided information on the characteristics of 1500 subjects with CHD who received immunoprophylaxis for RSV with palivizumab from 2000 to 2004. To our knowledge, the current analysis provides the first prospective epidemiologic report outside of a clinical trial on subjects with CHD who received prophylaxis with palivizumab. The impact of the pivotal trial and the 2003 revised AAP recommendations for RSV prophylaxis in infants with hemodynamically significant CHD is evidenced by the substantial increase in the number of subjects with cyanotic heart disease enrolled in the Registry and given prophylaxis over the 4 years [3, 6]. A greater than 50% increase in the number of subjects with hemodynamically significant CHD enrolled in the Registry was observed from the winter of 2002–2003 to 2003–2004. This also might reflect a stricter interpretation of the changing AAP guidelines by physicians such that prophylaxis was more restricted to subjects with hemodynamically significant CHD as opposed to any CHD. Our findings suggest that physicians, primarily pediatricians, prescribe palivizumab to subjects with CHD consistent with the AAP guidelines and labeled indications.

The present analysis shows that among registry subjects with CHD, there was a higher percentage of infants born after 35 weeks' gestation and weighing >2500 g when compared with all subjects enrolled in the registry [5, 15, 16]. As expected, the physician-reported prevalence of CHD among registry subjects (76.7 cases per 1000 registry subjects) is higher than the reported incidence of CHD ($\sim$10 cases per 1000 live births) [7]. This comparison is consistent with pediatricians selectively providing immunoprophylaxis to the small subset of infants born with these malformations, thus considering them to be at increased risk of complications from RSV.

The hospitalization rate for registry subjects with CHD was significantly higher than the rate of those without CHD. This finding is reflective of the higher risk that subjects with CHD have for RSV hospitalization, which is consistent with prelicensure data showing that palivizumab does not prevent all hospitalizations [8]. Nonetheless, the RSV hospitalization rates in those subjects with either cyanotic or acyanotic CHD who received palivizumab were low and decreased from the first to the fourth season. Although we did not examine this, the decrease in overall hospitalization rates and hospitalization rates among subjects with CHD was temporally associated with increased compliance with monthly injections over the 4 years of the registry.

Rates of RSV hospitalization for registry subjects with CHD, particularly in the last three seasons, are lower than the confirmed reports in the clinical trial of infants with hemodynamically significant CHD who received palivizumab (5.3%) [6]. However, data combined from the last two seasons show that more than 50% of registry subjects with CHD did not have hemodynamically significant disease, whereas this was an inclusion criterion for the clinical trial. Moreover, several factors regarding our collection of hospitalization data might have contributed to this difference. We speculate that the higher hospitalization rates among subjects with CHD in the first vs later seasons might have resulted from variability in the pattern of RSV epidemiology [13, 18] and registry-specific factors, such as changes in participating sites and investigators, variations in study populations, and disparity in hospital admission criteria over the four RSV seasons. Furthermore, physicians might have been less likely to hospitalize patients in

the latter seasons based on revised AAP guidelines and clinical trial results. Finally, we might have underestimated the hospitalization rate in registry subjects with CHD because only hospitalizations for which RSV was diagnostically confirmed were documented [15].

In conclusion, postlicensure experience with palivizumab in a cohort of infants and young children with CHD is generally consistent with the revised AAP guidelines and the clinical trial results for palivizumab. Clinical practice reporting shows increasing use in those with CHD, particularly those with cyanotic disease. Our data further suggest that cardiovascular malformations observed in subjects with CHD who receive palivizumab are characteristic of the congenital cardiac malformations seen in the general population. This analysis of the registry provides the largest report outlining the demographic and clinical characteristics of a cohort of infants with CHD receiving palivizumab and confirms the efficacy of palivizumab [6].

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