

Palivizumab prophylaxis against respiratory syncytial virus infection in patients younger than 2 years of age with congenital heart disease

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BACKGROUND: Respiratory syncytial virus (RSV) is a viral pathogen that causes annual epidemics of lower respiratory tract infection with substantial morbidity and mortality in young children, especially those with congenital heart disease (CHD). Palivizumab is the only immunoprophylaxis therapy approved for RSV infection in infants with hemodynamically significant acyanotic or cyanotic CHD.

OBJECTIVES: Identify the compliance rate with vaccination and study the effect of RSV vaccination on hospital admissions.

DESIGN: Retrospective descriptive study.

SETTING: Cardiac center.

PATIENTS AND METHODS: Patient data was obtained from outpatient clinic records, inpatient records, and a surgical database for the period from October 2010 to March 2016. Infants with hemodynamically significant CHD, cyanotic CHD and moderate-to-severe pulmonary hypertension were included in the study. Palivizumab 15/mg/kg was given monthly starting from October, the usual beginning of the epidemic season, with five doses in the first season and six doses in the remaining season scheduled for administration. Patients were interviewed at every clinic visit for any side effects during the previous month, occurrence of any RSV infection and any hospital admission. Selection criteria included RSV vaccination and absence of RSV disease. Patients were excluded if they had RSV infection or a repaired cardiac lesion.

MAIN OUTCOME MEASURES: Compliance rate, hospital admission frequency and period of stay.

SAMPLE SIZE: 530 during six seasons of RSV epidemics.

RESULTS: Fourteen patients (2.6%) developed RSV infection and 13 (2.5%) required hospital admission, but only one patient (0.1%) needed intensive care admission. There were no deaths related to RSV infection; however 11 patients died due to causes unrelated to RSV infection. The average compliance rate was 97%.

CONCLUSIONS: Palivizumab was well tolerated and effective in the prophylaxis of severe RSV infection in children with CHD. As in other studies of palivizumab prophylaxis, we observed a reduction in hospital admissions.

LIMITATIONS: Retrospective design.

CONFLICT OF INTEREST: None.

Respiratory syncytial virus (RSV) is a viral pathogen that produces annual epidemics.¹ The RSV season varies in different regions of the world. In Saudi Arabia the season extends from October to March, and the duration may vary each year.¹ RSV is one of the most important causes of hospitalization in children, particularly in those younger than 1 year of age in whom it causes substantial morbidity.² Studies from the United States reveal that RSV is the most common viral cause of death in children younger than 2 years of age, mainly in infants younger than 1 year of age.³ In addition, the effects of RSV may extend beyond hospitalization, since there is significant discussion about whether RSV bronchiolitis in infancy contributes to the development of asthma later in childhood.⁴⁻⁶ There is no vaccine currently available to prevent RSV infection. However, the anti-influenza drug oseltamivir together with anti-inflammatory therapies to treat severe RSV may alleviate discomfort and help patients to recover more quickly.⁵ Reinfection is common, even within one respiratory season.⁷ Therefore, it is essential that RSV prophylaxis is initiated to minimize the impact of RSV infection in vulnerable infants such as those with congenital heart disease (CHD). Palivizumab is a monoclonal antibody produced by recombinant DNA technology. RSV infection has frequently threatened CHD infants with congestive heart failure, cyanosis, or with pulmonary hypertension (PHTN). Monthly palivizumab (15 mg/kg IM) was safe, well tolerated, and effective for prophylaxis of serious RSV disease in young children with hemodynamically significant CHD.⁸ We report the impact of palivizumab in infants with hemodynamically significant CHD, cyanotic CHD and moderate-to-severe PHTN.

PATIENTS AND METHODS

Patient data was obtained from outpatient clinic records, inpatient records, and a surgical database for

the period from October 2010 to March 2016 at King Abdulaziz Cardiac Center (KACC), Riyadh. IRB approval was obtained from King Abdullah International Medical Research Center (KAIMRC) RC17/338/R. The patients were selected for palivizumab prophylaxis according to the criteria defined by the American Academy of Pediatrics' (AAP) Policy Statement Guidance 2009, updated 2014.^{9,10} Exclusion criteria were RSV positivity, and refusal to be enrolled. In addition, any patient who underwent surgical repair for CHD during the season usually failed to complete the prophylaxis if they had no residual lesions and thus they were eliminated from the study group. The compliance rate was measured by the total number of doses received divided by the total number of doses required.

The RSV team consisted of two doctors, three nurses, and one clinic coordinator. Data were entered into an electronic database (Apollo or Best systems). Five palivizumab doses 15/mg/kg/dose were scheduled to be given monthly starting from October 2010 to February 2011. In seasons two to six a total of six doses scheduled to be given as per our infectious disease recommendations, due to an extended RSV infection season. Patients were interviewed at every clinic visit for any adverse effects in the previous month side effects, RSV infection and for any hospital admission.

RESULTS

Over the six RSV seasons, we studied 530 patients who received palivizumab prophylaxis (**Table 1**). Gender distribution was approximately equal. Acyanotic CHD, which is hemodynamically significant and presents with heart failure symptoms and signs, occurred in slightly more than half of patients (52.5%). Among those who received prophylaxis, 14 (2.6%) developed RSV infection. Thirteen patients (2.5%) required hospital admission with one patient (0.1%) requiring admission to the

Table 1. Clinical information on infants for each of six seasons of respiratory syncytial virus (n=530).

Season	No of patients during each season	Cyanotic	Acyanotic	No of doses per season	No of patients with RSV infection after prophylaxis	No of patients needing hospital admission
2010-2011	52	28	24	52	3	2 (1 needed ICU)
2011-2012	70	28	42	70	3	3
2012-2013	93	46	47	93	3	3
2013-2014	138	66	72	124	1	1
2014-2015	77	43	34	77	3	3
2015-2016	100	41	59	100	1	1
Total	530	252	278	516	14	13

intensive care unit (ICU). There were no deaths related to RSV infection, however, 11 patients died due to causes unrelated to RSV infection. The average compliance rate for the six seasons was 97%.

In season one (2010-2011), of 52 patients, 28 (54%) patients had cyanotic CHD, while 24 (46%) had acyanotic CHD. Twenty-two patients completed 5 doses, 13 patients completed 4 doses, 7 patients received 3 doses, 8 patients received 2 doses and 2 patients received 1 dose. Ten patients completed their doses outside the center after the first dose. Less than 5 doses were due to late inclusion, completion of surgery, financial reasons, and non-compliance. Three patients developed RSV infection. Two patients were admitted to hospital with RSV positive bronchiolitis for 5 days, with no required stay in ICU. The third patient had a prolonged hospital stay due to end-stage heart failure (dilated cardiomyopathy); however, the repeat RSV test was negative. No adverse side effects due to palivizumab were reported. There were three deaths (one RSV-negative patient with Down syndrome and atrioventricular septal defect [AVSD] because of pneumonia; one patient with complex cyanotic CHD status after a modified Blalock-Taussig shunt with a blocked shunt; one RSV-negative patient with dilated cardiomyopathy in end-stage heart failure because of cardiopulmonary arrest). There were no deaths related to RSV infection.

In season two (2011-2012), of 70 patients analyzed, 28 (40%) had cyanotic CHD, while 42 (60%) had acyanotic CHD. Twenty-eight patients completed 6 doses, 13 patients received 5 doses, 14 patients received 4 doses, 7 patients received 3 doses, 5 patients received 2 doses and 3 patients received 1 dose only. Nine patients received only their first dose, but completed the remaining doses outside of KACC. Three patients had proven RSV infections; all had acyanotic CHD and were hospitalized for 3-4 days with a smooth course with no ICU admission. No adverse side effects due to palivizumab were reported. Patients who received doses outside of our center were confirmed by the clinic coordinator. There were no deaths during this season.

In season three (2012-2013), of 93 patients analyzed, 46 (49.5%) had cyanotic CHD, while 47 (50.5%) had acyanotic CHD. Twenty-seven patients completed 6 doses, 16 patients completed 5 doses, 13 patients completed 4 doses, 17 patients completed 3 doses, 14 patients completed 2 doses, and 6 patients completed one dose. After the first dose, ten patients received a few of their remaining doses outside of our center, which was confirmed by the clinic coordinator. Two patients presented with low-grade fever but no other

adverse effects were reported. There were two deaths unrelated to RSV. Three patients developed RSV bronchiolitis after palivizumab and required admission from 5 to 9 days with 1-2 days of oxygen therapy. There were no ICU admissions in the palivizumab group. The total number of patients who missed doses was 15, due to intercurrent illnesses and poor compliance.

In season four (2013-2014), of 138 patients analyzed, 66 (47.8%) had cyanotic CHD, while 72 (52.2%) had acyanotic CHD. Seventy patients completed 5 doses, 42 patients completed 4 doses, 5 patients completed 3 doses, 4 patients completed 2 doses, 3 patients received 1 dose, 5 patients were excluded as they underwent cardiac surgeries with no residual lesions. After the first dose, eight patients received their remaining doses outside of our center and were confirmed by the clinic coordinator. One patient developed RSV-positive bronchiolitis and required treatment for 7 days but with no need for ICU admission. There were three deaths not related to RSV infection: the first one was a patient with double inlet left ventricle (DILV), transposition of the great arteries and coarctation of aorta who died due to cardiac arrest; the second was a patient with DILV status after patent ductus arteriosus (PDA) ligation, and died with septic shock; the third one was a patient with right isomerism, AVSD, pulmonary stenosis and small left ventricle who died with septic shock.

In season five (2014-2015), of 77 patients, 43 (55.8%) had cyanotic CHD, while 34 (44.2%) had acyanotic CHD. Forty-four completed 5 doses, 20 patients completed 4 doses, 10 patients completed 3 doses, 2 patients received 2 doses, 1 patient received 1 dose; 3 patients were excluded as they underwent cardiac surgeries with no residual lesions. After the first dose, six patients received a few of their remaining doses outside of our center, which were confirmed by the clinic coordinator. There was one death unrelated to RSV (a patient who was diagnosed with Down syndrome, unbalanced AVSD and PHTN, and died in another hospital). Three patients developed bronchiolitis: two of them were rhinovirus positive, one had human coronavirus. They required admission from 4-10 days with 1-2 days of oxygen therapy. There were no ICU admissions.

In season six (2015-2016), of 100 patients, 41 (41%) patients had cyanotic CHD, while 59 (59%) presented with acyanotic CHD. Sixty-three patients completed 5 doses, 7 patients completed 4 doses, 7 patients completed 3 doses, 8 patients completed 2 doses, 15 patients completed 1 dose; 3 patients discontinued treatment as they had cardiac surgery with no residual lesions. After the first dose, six patients received a few of their remaining doses outside of our center, which

was confirmed by the clinic coordinator. There were two deaths: one patient, diagnosed with dilated cardiomyopathy and severely depressed cardiac function, died due to cardiac arrest; the other one had double outlet right ventricle, pulmonary atresia and PDA, and died with septic shock. One patient developed RSV positive bronchiolitis.

DISCUSSION

This is the first study in Saudi Arabia of palivizumab in patients with CHD according to AAP's revised recommendation from 2009 and the Saudi Congenital Heart Group. We used palivizumab for hemodynamically significant CHD, cyanotic CHD and PHTN patients. The results of this study showed outcomes that were consistent with international studies of palivizumab prophylaxis. The results were consistent with the results that Feltes et al reported in their randomized, double blind, placebo-controlled trial.^{8,9} Further, in our study, the safety of palivizumab in patients with CHD was similar to that observed in other pediatric populations; monthly palivizumab (15 mg/kg IM) was safe, well-tolerated, and effective for prophylaxis of serious RSV disease in infants and young children with hemodynamically significant CHD.¹¹ Consistent with other studies, we observed a decreased length of hospital stay. No ICU admission was required for the 11 RSV-positive patients during the six seasons. Palivizumab was not administered during acute RSV positive status because it has been shown that there is no beneficial clinical effect of this treatment on established RSV disease such as reducing the rate of mechanical ventilation and mortality in children affected with RSV.² Compliance with monthly palivizumab injections is the key for successful RSV pro-

tection. Several studies investigated the association of administration of prophylaxis through monthly home visits by a health professional with parental compliance with therapy; most of the home-based programs were associated with higher compliance rates compared with clinic or office programs.¹² In our study, we designed our own RSV team who counselled all the parents, including counseling by telephone. We suspect that the high average compliance rate (97%) was related to this dedicated RSV team and the meticulous follow-up of patients. Few patients had insurance issues on their medical coverage. There were no serious side effects, although a few patients reported that they developed mild fever after palivizumab administration. In our study the rate of RSV infection in the group who received the Palivizumab was 3%. While the hospital admission was 2.5% with 0.1% of the patients requiring ICU admission, there were no deaths related to RSV infection; however, 11 patients died to causes unrelated to RSV infection.

In conclusion, palivizumab is safe, well tolerated and effective in the prophylaxis of severe RSV infection in patients with CHD. As in other studies of palivizumab prophylaxis, we observed a reduction in hospital admissions. Two of the major success factors were the dedicated RSV team and the continuous parent counseling, both of which improved compliance.

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