JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Effectiveness of palivizumab immunoprophylaxis in infants with respiratory syncytial virus disease in Colombia

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Abstract

Introduction: Respiratory syncytial virus (RSV) is one of the most important childhood infections. Objective: To evaluate the effectiveness and safety of palivizumab immunoprophylaxis in preterm infants at a high risk of severe respiratory syncytial virus infection during the RSV season in Colombia.

Methodology: A prospective observational non-comparative multicenter study in six Colombian cities. At the beginning of the RSV infection season, palivizumab prophylaxis, up to five doses, was administered to infants born at ≤32 weeks of gestation, infants younger than six months, infants under one year of age with bronchopulmonary dysplasia (BPD), infants one year or less of age with hemodynamically significant acyanotic and non-acyanotic congenital heart disease (CHD), and with follow-up during the immunoprophylaxis until one month after the last dose.

Results: The study enrolled 600 patients, 91.8% of which were born at ≤ 32 weeks of gestation. BPD was observed in 54.9% of infants. 49% were born at < 32 weeks gestation and presented BPD. 6.9% had hemodynamically significant acyanotic and non-acyanotic CHD 53.3% received three or more doses of palivizumab. The mean interval between doses was 39.6 days. 1.8% of patients were hospitalized due to a confirmed RSV infection. Overall mortality was 1.2%, whereas the mortality by RSV in infants undergoing prophylaxis was 0.2%.

Conclusions: Palivizumab was a clinically effective, well-tolerated treatment in the Colombian population. The safety profile of palivizumab reflects the findings from previous studies in developed countries.

Key words: Palivizumab; prophylaxis; respiratory syncytial virus; lower respiratory tract infection.

J Infect Dev Ctries 2021; 15(11):1708-1713. doi:10.3855/jidc.12561

(Received 17 February 2020 – Accepted 13 February 2021)

Introduction

In children younger than five years old, lower respiratory tract infections (LRTI) caused by a respiratory syncytial virus (RSV) constitute the leading cause of morbidity and mortality worldwide [1,2]. According to recent publications, its prevalence is approximately 33.1 million cases, and 3.4 million hospitalizations per year; of these, 91% occur in developing countries. In 2015, the estimated mortality for children less than five years old was 48,000-74,500, and 20,700-36,200 in children younger than 6 months, with 99% of these deaths occurring in developing countries [3,4]. In Colombia, Piñeros *et al*. [5] reported a global incidence of 30% RSV positive tests in 717 infants under one year of age hospitalized with LRTI. In the different cities, the range of variability of RSV positivity was 23.8% to 49%. 59 patients (8.2%) were high-risk patients with extreme prematurity (below 32 weeks of gestational age) or bronchopulmonary dysplasia (BPD). The RSV test was positive in 28.8% of these patients, a proportion similar to the general population.

A recent review of the epidemiology of LRTI in Latin America [6] including 74 studies illustrated that in infants less than one year old, RSV was the etiologic agent in 36.5% (95% CI = 28.5-44.9) of the cases. In neonates hospitalized with LRTI, 41.5% (95% CI = 32.0-41.4) were associated with RSV. Infants with risk factors, such as prematurity, bronchopulmonary dysplasia (BPD), and congenital heart disease (CHD), stay 75% longer in the hospital, including days spent in the Pediatric Intensive Care Unit (PICU) (12.8 days *vs*. 7.3 days without risk factors). These infants have twice the risk of requiring mechanical ventilation (24% *vs*. 11.1%).

Another study by Szabo *et al*. [7], analyzes the RSV mortality rates and their variations according to the specific risks. The RSV mortality rate for infants without any risk factors was < 1%. For preterm infants < 36 weeks, the rate was 0-6.1%. For infants with BPD, it was 3.5-23%, with CHD 2-37%, and with RSV nosocomial infection 0-12.2%. When the infant required PICU support, the RSV mortality rate ranged from 1.1-33%. Other risk factors for RSV mortality include not breastfeeding, crowding, history of atopy, and maternal smoking, which are common factors in developing countries [8,9].

The availability of a humanized RSV monoclonal antibody such as palivizumab (brand name Synagis) has provided an effective intramuscular prophylactic intervention for infants at high risk of developing RSV disease. This has resulted in significant reductions in negative health outcomes such as length of hospitalizations, the incidence of admission to intensive care units, supplemental oxygen requirements, and hospitalization due to moderate/severe lower respiratory tract illness [10]. Wegzyn *et al*. [11] showed a 55% reduction in the incidence of RSV hospitalizations with the use of palivizumab in children with high risk (prematurity and the presence of BPD). Although the safety and effectiveness profile of palivizumab has been established in controlled clinical trials and real-life settings, there is still a paucity of data in the setting of usual clinical practice, especially in developing countries where the burden of disease is higher [12]. Some studies describe the relation in the cost-effectiveness of this medication; the more targeted the risk group, the more likely the immunoprophylaxis was cost-effective [13]. This is important to reduce the use of healthcare resources given by hospitalizations attributable to respiratory infections, or sequelae [14].

Even though the effectiveness of palivizumab has been demonstrated in different studies, complete information on the use of prophylaxis in Colombia is unknown. Castillo *et al*. [15] found that in seven Latin American countries (464 total infants), palivizumab prophylaxis appeared effective and had a good safety profile in this population; however, only a few cities from Colombia were included in his study, with only 147 Colombian patients, making their results non-representative of the entire country.

This is an observational, non-interventional, post-marketing, and uncontrolled study. The aim was to evaluate the effectiveness of palivizumab as a method of immunoprophylaxis in preterm infants with a high risk of severe RSV infection (infants born at ≤ 32 weeks of gestation, infants with BPD, or infants with CHD) during the RSV season in Colombia. A secondary objective was to evaluate the safety of this treatment in a real-life setting reflecting routine care.

Methodology

This is a prospective observational study of a cohort of infants, who were treated in high complexity hospitals in six primary cities of Colombia. The patients were infants, who received palivizumab immunoprophylaxis according to the Colombian Neonatal Association guidelines during the RSV season while attending a Kangaroo Mother Care Program [16]. Patients included were: i) Infants born at ≤32 weeks of gestation who were younger than six months of age at the beginning of the RSV infection season; ii) children under one year old with BPD who had received medical treatment in the last six months; and iii) children 12 months of age or younger with hemodynamically significant cyanotic and non-cyanotic CHD (pulmonary hypertension or heart failure in medical treatment). Subjects were excluded if any of the following criteria were present: major congenital malformation, chronic pulmonary disease other than BPD, contraindication to palivizumab, patients who received another immunoglobulin preparation, or any other condition that according to the investigator represented an obstacle for study conduction or unacceptable risk to patients. The decision to prescribe palivizumab to a subject was separated from the decision to include the subject in the study. All patients recruited received at least one dose.

Initially, this study was planned to enroll an approximate total of 200 patients from different centers in Bogotá, Colombia, and thereafter was spread to other main cities in Colombia (Barranquilla, Bucaramanga, Cali, Medellín, Cartagena, and Pereira), adjusting the final sample size to 600 patients. Each patient was followed through the immunoprophylaxis. The recruitment period lasted 2 years.

Prophylaxis was administered monthly throughout the RSV season with a maximum of five doses. It was administered intramuscularly at a dose of 15 mg/kg. Visits were done each month while the infant received prophylaxis. The subjects were followed up to 30 days after receiving the last dose. Epidemiological and clinical data, information about patient adherence, hospitalization details, and safety data were collected. A physical examination was performed at each in-office study visit. Adverse events and hospitalizations that occurred since the previous visit were also recorded.

If the patient was hospitalized due to a respiratory infection, in order to determine if they had an RSV infection, an immunofluorescence rapid test in nasopharyngeal secretions was performed (BIO-RAD, Monofluotm Screen R.S.V. 80 Tests Detection Du Virus Respiratoire Syncytial Par Immunofluorescence Directe. IVD). Although there are more complex and specific tests to diagnose RSV, they are more expensive and more difficult to perform, and they were not available in all the study sites. A lower respiratory tract infection was diagnosed by the presence of respiratory symptoms, which included a runny nose, cough, hoarseness, difficulty breathing, nasal flaring, intercostal retractions, sternal retraction, inspiratory or expiratory stridor, or evidence of respiratory compromise on physical examination with the presence of wheezing, rhonchi, or murmur tubal lung auscultation. If a positive RSV test was confirmed, the hospitalization data and outcome were registered.

Patients stopped receiving treatment with palivizumab if the subject's parent/guardian voluntarily withdrew from the study, or the patient had a serious adverse event where the risks of continuing the study outweighed the benefits. Even if the treatment was discontinued for any reason, subjects were observed during the study with parental agreement.

The main outcome was established by the hospitalization rate due to confirmed RSV infection and mortality rate secondary to this infection. Safety was an important consideration during this study, assessed by the presence of serious adverse events. These were defined as any experience that causes death, a risk to life, disability, hospitalization (or prolongation of hospitalization), or congenital malformation. An unexpected medical reaction or event was also considered a serious adverse event. Non-serious adverse events were defined as any unfavorable medical event that occurs in a subject of a clinical study to whom a pharmaceutical product was administered, which does not necessarily have a causal relationship with that treatment. They can be any unfavorable or unintended signs, including an abnormal laboratory finding, or symptoms or illnesses temporarily associated with the use of a medicinal product (research) whether or not related to it, which do not meet serious adverse event criteria [17].

Before entering the study, the patients' parents or guardians signed an informed consent form giving authorization for the investigator to use and/or disclose the patients' personal health data. The research ethics committee of each of the participating institutions approved the study.

Statistical analysis

The intervention variable (palivizumab immunoprophylaxis) was summarized as the doses administered during the follow-up period. A description of administered doses and application intervals between doses is shown. For continuous variables, summary statistics (n, mean and standard deviation) and 95% confidence intervals were calculated. For categorical data, absolute frequency, relative frequency, and 95% confidence intervals were calculated. Safety was measured by the incidences of serious and non-serious adverse events.

Results

The study enrollment was completed in 24 months. Although 600 patients from different cities were included in the study, the final analysis was performed on 596 patients. Four of the patients withdrew their informed consent.

Demographic and other baseline data were described. Of the 596 infants, 282 (47.2%) were female, and 314 (52.8%) were male. A total of 547 infants (91.8%) were born at ≤ 32 weeks gestation and were younger than six months of age at the beginning of the RSV season. BPD was observed in 328 (54.9%) infants, and 41(6.9%) suffered from hemodynamically

Table 1. Demographic characteristics found at enrollment.

Characteristics	n	Average	SD
Gestational age at birth (weeks)	596	30.2	2.6
Corrected gestational age (weeks)	591	36.5	5.2
Birth Weight (grams)	595	1420	483.8
Birth Height (cm)	575	39.2	4.3

SD: Standard deviation.

significant cyanotic or non-cyanotic CHD (pulmonary hypertension or heart failure with medical treatment). A total of 291 infants (49%) were born at < 32 weeks gestation and had BPD. Table 1 shows other demographic characteristics of patient enrollment along with their birth date.

Dose frequency per patient is shown in Table 2. Three doses of palivizumab were administered to 50% of patients. Only 7 patients received five doses (1.1%). Table 3 shows the proportion of patients to the number of doses. More than half of the patients (53.3%) received at least three doses.

The mean intervals between doses in days were 39.6 days (SD = 37.4) between doses 1 and 2, 40.7 days (SD = 21.4) between doses 2 and 3, 56.5 days (SD = 49.3) between doses 3 and 4, and 37.3 days (SD = 21.4) between doses 4 and 5. We found that 58.7% of all doses were received with an interval of fewer than 35 days while the rest were received with an interval greater than 35 days (41.3%).

The proportion of infants who were re-hospitalized for general reasons was 14.8% (88), including respiratory and non-respiratory causes. Eleven patients (1.8%) were hospitalized due to a confirmed RSV infection. There was only one case with a doubtful result (Table 4). Of the 11 patients hospitalized for RSV infection, 6 (54.5%) had bronchopulmonary dysplasia (BPD) as a predisposing factor, and 4 (36.4%) received mechanical ventilation. The average infant hospitalization time was 38.2 days (SD=23.3 days).

A total of 103 adverse events were reported during the study. Of these, 95 (92.2%) were serious while the other 8 (7.7%) were reported as non-serious adverse events. There were seven deaths and 88 hospitalizations related to general causes. Only one of the patients who died had a positive RSV test. The general mortality was 1.2% (7/596), and due to a variety of causes: BPD with left ventricular failure, multisystem failure, bacterial pneumonia and sepsis, bacterial pneumonia, respiratory arrest, cerebral hemorrhage, and over-infected bronchiolitis. Specific mortality by RSV in infants undergoing prophylaxis was 0.2% (1/596) due to over infected bronchiolitis.

Table 2. Distribution of the number of doses (n = 1,405).

Number of doses	Frequency (%)
1	132 (22.15)
2	146 (24.50)
3	298 (50.00)
4	13 (2.18)
5	7 (1.17)
Total	596 (100.00)

Table 3. The proportion of patients vs the number of doses.

Number of doses	Patients (%)
At least one dose	596 (100.00)
At least two doses	464 (77.85)
At least three doses	318 (53.35)
At least four doses	20 (3.35)
At least five doses	7 (1.17)

Discussion

RSV is the most common etiologic agent of acute lower respiratory infection in children under 2 years of age, having its maximum incidence between 2 and 6 months [18]. In this study, more than 90% of patients were extremely preterm (< 32 weeks of gestational age), and close to 50% had bronchopulmonary dysplasia (BPD). This makes participants a very high-risk population for RSV infection.

In an epidemiologic study on RSV conducted in Colombia [5], high-risk infant patients (mainly preterm with BPD) without prophylaxis, had more severe morbidity rates compared to the data described for developed countries. They had an average hospital stay of 8.6 days per patient, a PICU admission of 52.9%, an average PICU stay of 8.3 days, a mechanical ventilation rate of 41.2%, and a mechanical ventilation duration of 3.8 days, with a mortality rate of 5.8% [7]. This higher morbimortality in Latin American countries is also evident in other studies [8,9]. In Argentina, the RSV average rehospitalization rate in high-risk patients without prophylaxis was 26% for 4 years. This rate was variable during the different years with a range of 18-38%. The average hospital stay was 18 days, with a mechanical ventilation rate of 34%, an average mechanical ventilation use of 16 days, and a mortality rate of 1.3% [8]. In Mexico, 79% of hospitalized infants with RSV had risk factors, 16.1% required mechanical ventilation, and the RSV-specific mortality was 4.4%. The mortality in infants with risk factors was greater

Table 4. Frequency of patient hospitalization for RSV and proportion of tests performed.

RSV Test	Frequency (%)	95% CI
Positive	11 (12.5)	(6.4-21.2)
Negative	61 (69.3)	(58.5-78.7)
Doubtful	1 (1.1)	(0.2- 6.1)
Not related to LRTI*	15 (14.7)	(9.8-26.5)

* Test not performed due to Non-Respiratory Cause Hospitalization.

(6.6%) in comparison with that of infants without risk factors (2.3%) [9]. In another recent Mexican study of a cohort of 294 preterm infants, the RSV admission frequencies were estimated to be 13.6% in BPD, 16.5% in CHD, and 4.1% in otherwise healthy preterm infants [19]. In another study, children with risk factors such as premature birth, a pre-existing respiratory disease, or CDH, have higher morbimortality if coinfected with adenovirus (RSV mortality of 1.1% and 2.7% in co-infection with adenovirus) [10].

Depending on the real rate of rehospitalization without prophylaxis in each geographical area, the impact of palivizumab could increase by preventing more hospitalizations and improving cost-effectiveness. Cody Meissner *et al*. [20] showed that the benefit of immunoprophylaxis was an overall reduction in RSV hospitalization rates of 4.4% (9.7% placebo *vs*. 5.3% palivizumab; $p = 0.003$). A study in Israel showed that the duration of hospital stays, oxygen supplementation, and PICU admissions was significantly decreased with the use of palivizumab. Patients who did not receive the medication before hospitalization had the worst course of the illness [21].

Our hospitalization rate of 1.8% in infants with prophylaxis is similar to the rates of studies published in developed countries [11]. In Latin America, there are few studies about real-life Palivizumab prophylaxis. In a study in Brazil, of 104 infants with CHD who received palivizumab, 9.6% were hospitalized with LRTI, with no cases of RSV positivity [22]. In a Latin American study with 458 infants with prophylaxis, the RSV hospitalization rate was 2.9 per 100 patient-years [15].

Using our hospitalization rate of 1.8% in infants with prophylaxis, the hospitalization rate reduction would be 85.6% regarding the impact study [12] (12.5% hospitalization rate for non-prophylaxis), and 93.1% regarding the study from Argentina [23] (26% average hospitalization rate in infants without prophylaxis). These results compare very well to other reported rates in similar follow-up studies [6]. The specific RSV mortality in infants undergoing prophylaxis in our study was 0.2%. It is very low, compared to the reported mortality of 5.8% in the subgroup of unprotected high-risk Colombian infants in the epidemiologic study [5], or other reported mortalities [8,9].

Conclusions

In many recent papers, the effectiveness of the use of palivizumab as immunoprophylaxis for children with RSV risk factors is clear, given the decrease in the hospitalization rates and future respiratory complications. Thus, the interest is in the cost-effectiveness of the use of palivizumab as immunoprophylaxis. According to this, palivizumab prophylaxis cost varies depending on the population and setting, and preterm infants were the most cost-effective patients to be treated, which was expected given their higher risk for RSV [24,25].

This study is one of the largest studies performed in Latin America, and the biggest conducted in Colombia. The fact that the study covered several main cities in the country provides an improved reflection of the use of palivizumab in our environment. Even though a few patients with heart disease were included, limiting the applicability of the results obtained for this population, the results of this study indicate that palivizumab is a clinically effective and well-tolerated treatment in the Colombian population. Furthermore, the safety profile of palivizumab in this study reflects the findings from previous studies, most of them done in developed countries [25–27].

The main limitation of the study consists in the lack of simultaneous local comparative patients that did not receive prophylaxis, making it difficult to establish a nonbiased effectivity. Another limitation is the low number of doses received by each patient, and the longer interval between doses. It is hypothesized that if the number of doses is increased to five and the interval between doses is always lowered to less than 35 days, the effectiveness of the intervention will be improved even more.

Acknowledgments

We thank the following for their contribution to this study: staff neonatologists and nurses of the NICU and all the coordinators of the follow-up programs of neonatal high-risk patients.

Funding

This study was financed by Abbvie SAS in Colombia through a grant to the Colombian Neonatal Association.

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Conflict of interests: Juan Gabriel Piñeros, Clara Galvis, and Oscar Ovalle have participated as paid speakers for Abbvie SAS. All other authors declare no conflicts of interest.