ORIGINAL ARTICLE

Prevention of syncytial respiratory virus infection with palivizumab: descriptive and comparative analysis after 12 years of use

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ABSTRACT

BACKGROUND: The use of palivizumab has been recommended to prevent syncytial respiratory virus (SRV) infection in vulnerable children.
METHODS: We performed a retrospective study of hospital admissions for bronchiolitis from 2000 to 2012 in the context of a prevention study with palivizumab in at-risk newborns.
RESULTS: A total of 952 children (59.5% males) were admitted due to bronchiolitis. Admissions occurred in younger children in the SRV+ cases compared to the SRV- cases (P<0.001). Additionally, 641 children were treated with Palivizumab at our service. Sixty of these children (9.8%) were admitted due to bronchiolitis and SRV was detected in 22 of them (3.4%). Fifty (7.8%) had underlying diseases, 6 (0.9%) presented with a history of perinatal infection and 20 (3.12%) had been part of a multiple birth. The treated children with some additional risk factor presented a greater risk of admission due to bronchiolitis (OR=1.99, P=0.045); however, this was not observed for admissions due to SRV (P=0.945).
CONCLUSIONS: Children treated with Palivizumab showed a lower rate of SRV infection, despite having more risk factors associated with a higher risk of infection or complications.

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KEY WORDS: Palivizumab - Respiratory syncytial virus infections - Child - Prevention and control - Antibiotic prophylaxis - Bronchiolitis.

Respiratory syncytial virus (SRV) is the commonest pathogen causing acute respiratory infections in infants and young children. It is a very common reason for primary care consultation and the main cause for hospital admissions due to respiratory disease (bronchiolitis and pneumonia) in those under 1 year of age. Near 80% of children contract the infection before 2 years of age and 0.5-2% of those affected have to be hospitalized as a result.[1]

SRV in Spain presents a seasonal pattern with an increase during winter months, primarily between September and March.[2] It is the main causal agent of bronchiolitis in children, especially in those aged 2-6 months; 50-80% of cases are attributed to it and it is the most commonly isolated virus in patients with simple infection (80%).[3, 4]

Immunity does not occur after infection and thus reinfections are common, as the child gets

older. Moreover, it is known that around 40-50% of children hospitalized due to bronchiolitis have recurrent episodes of wheezing in the first years of life.[5] All this generates a considerable impact in terms of morbidity and social and healthcare costs.[1] This impact increases in premature children, those with heart diseases, those who are immunodeficient and in patients with severe underlying lung diseases; such patients are susceptible to suffering much more seriously from disease due to SRV and have hospitalization rates greater than 13%.[5-7]

Prevention of SRV infection is based on hygiene measures and on the use of specific monoclonal antibodies (Palivizumab, Synagis®, Abbott Laboratories, Abbott Park, IL, USA).[5] However, the high economic cost of this product has generated controversy in terms of benefit-cost ratio for administration. A considerable number of studies and reviews have been carried out with an aim to establish the most suitable criteria in these risk groups. From a clinical point of view, reduction of mortality due to SRV has been proved to be the most valid criterion; however, in developed countries, mortality due to SRV occurs so rarely that much larger samples must be collected to reach a conclusion. Therefore, the benefit of Palivizumab is measured by the reduction in the number of hospitalizations due to SRV.[7] Taking into consideration the American guidelines, the Spanish Society of Neonatology (SENeo) reviewed these indications in it 2015 publications.[7] Furthermore, it has been responsible for various multicentre studies compiled by the IRIS group: Flip (case-control multicenter study)[8] and Flip2 (cohort study).[9] Moreover, these studies have been able to clarify the indications for the most controversial group in our environment: premature infants of 32-35 weeks off gestational age (GA), (age group with the greatest variability in prescriptions). Three significant risk factors have been established and they can be divided into major and minor factors. The major factors are: chronological age under 10 weeks at the start of the season or being born in the first 10 weeks of the season; having at least one sibling who attends school or daycare; or going to daycare themselves. The minor factors are: history of tobacco use in the mother during pregnancy;

male gender; family history of wheezing. These studies conclude that, in our environment, passive immunoprevention with Palivizumab for premature infants of 32-35 weeks GA would be very recommendable in the presence of 2 major risk factors and recommendable in the presence of 1 major and two minor risk factors. The aim of the study is to describe and to compare the characteristics of patients admitted because of bronchiolitis, as well as analyze separately those who received palivizumab and those who did not.

Materials and methods

A retrospective study of the 2000-2012 period was carried out in the tertiary San Cecilio Hospital, Granada, Spain. They registered all patients admitted with a diagnosis of bronchiolitis and who were treated with palivizumab in this period. The following variables were included for hospital admissions: birth weight, gestational age, gender, number of siblings, age at admis-

TABLE I.—*General characteristics for patients with bronchiolitis hospitalized in the 2000-2012 period.*

Parameter	Gestational age (weeks)	Hospital admissions due to bronchiolitis (N.=952)
Birth weight, g	<28	875±113
	28-31	1432±253
	32-35	2318±522
	36-40	3119±517
	All	3043±623
General age of hospitalization Due to bronchiolitis (days)	<28	205±70
	28-31	155±130
	32-35	156±159
	36-40	118±112
	All	123±120
General age of hospitalization due to bronchiolitis SRV+, days	<28	–
	28-31	159±104
	32-35	121±139
	36-40	105±100
	All	107±109
General hospitalization stay due to bronchiolitis, days	<28	6.5±1.2
	28-31	9.7±4.3
	32-35	7.4±5.0
	36-40	6.8±4.2
	All	6.9±4.2
General hospitalization stay due to bronchiolitis SRV+, days	<28	–
	28-31	11.0±4.3
	32-35	6.9±3.5
	36-40	7.0±4.0
	All	7.1±4.1

TABLE II.—*General characteristics for patients treated with palivizumab in the 2000-2012 period.*

Parameters	Gestational age (weeks)	Patients treated with palivizumab (N.=641)
Birth weight (g)	<28	899±133
	28-31	1379±350
	32-35	1856±377
	36-40	3026±545
	All	1784±654
Age on admission in palivizumab patients, days	<28	200±110
	28-31	204±104
	32-35	139±109
	36-40	126±81
	All	162±107
Age on admission in palivizumab patients with SRV+, days	<28	–
	28-31	156±115
	32-35	117±111
	36-40	65±34
	All	121±105
Hospital stay in palivizumab patients, days	<28	5.8±3.2
	28-31	9.8±4.1
	32-35	7.1±4.1
	36-40	10.8±4.0
	All	8.0±4.2
Hospital stay in palivizumab patients with SRV+, days	<28	–
	28-31	10.7±4.7
	32-35	7.3±3.0
	36-40	15.1±2.1
	All	9.2±4.2

sion, number of days of stay, positive SRV determination, Palivizumab administration, and presence of other diseases. Tables I and II show the characteristics of patients treated with palivizumab and admitted to hospital with bronchiolitis.

Palivizumab immunoprophylaxis

Palivizumab is administered in a monthly dose between the months of October to March (SRV risk period), up to 5 doses. Included in the administration protocol, all infants less than 28 weeks gestational age and chronological age less than 12 months at the beginning of the period of risk for SRV, 29-32 weeks gestational age and chronological age less than 6 months at the beginning of the period of risk for SRV, children aged under 2 years with bronchopulmonary dysplasia, neuromuscular disease, chromosomal abnormalities and congenital heart disease. Patients were excluded after refusal of parents or legal guardian to participate in the study. Released

from the Hospital Ethics Committee was requested and the patient's rights to confidentiality is safeguarded.

Bronchiolitis diagnosis

Definitions used is a disorder most commonly caused in infants by viral lower respiratory infection; it is characterized by acute inflammation, edema and necrosis of epithelial cells lining small airways, increased mucus production, and bronchospasm. We consider end point the severity of bronchiolitis, in terms of Hospital admission.

The following variables were included in the review of medical histories of children treated with palivizumab: birth weight, GA, years of palivizumab, presence of other conditions. We also checked whether these patients had later been admitted due to bronchiolitis, assessing the time between Palivizumab administration and the date of admission, the number of days they stayed in hospital and whether SRV was present in their samples or not. SRV detection was performed by the microbiology service through PCR in nasopharyngeal aspirate.

Statistical analysis

A descriptive study of the two patient groups (treated and untreated) was carried out for all patients and by gestational age group. Normal distribution of quantitative variables was checked using the Shapiro-Wilk test. Patient characteristics were compared using Student's t-test, the Mann-Whitney U-test, the χ^2 test and Fisher's exact test. Differences were considered to be statistically significant when $P<0.05$. All the analyses were performed using SPSS for Windows, v. 13.0 (SPSS Inc., Chicago, IL, USA).

Results

Hospital admissions due to bronchiolitis in the 2000-2012 period

During the study period, information was compiled from 952 pediatric patients who had been admitted with a diagnosis of bronchiolitis, 566 (59.5%) of whom were male. Two percent (17/855) were under 32 weeks GA and 11.4%

(98/855) were ≤35 weeks GA. Mean GA was 38.4 weeks (range: 25-43). Patient characteristics by GA group are shown in Table I. Mean birth weight was 3043.6 grams. Of all the patients included, 531/900 (59%) were SRV+. The mean age at admission of patients admitted for bronchiolitis was 123 days, while the average age at admission of SRV+ patients admitted for bronchiolitis was 107 days. Children were admitted at a younger age in SRV+ cases than in SRV- cases (P<0.001). Furthermore, late pre-term births and term births were younger on admission (118 days in those ≥36 weeks GA vs. 158 days in <36 weeks GA, P=0.002).

Mean hospital stay was 6.9 days in children admitted due to bronchiolitis. Mean hospital stay was 6.7 days among the children with SRV-, while the mean stay was 7.06 days in SRV+ children. This means there were no significant differences between SRV+ and SRV- children (P=0.417).

The mean number of siblings was 0.94 per patient. Children with a sibling were admitted at a younger age (mean: 114.7 days of age) than those without siblings (mean: 137.1 days of age, P=0.007). A slight increase was observed in the length of stay in children with siblings compared to those without siblings (7 vs. 6.6 days); however, these differences were not significant (P=0.188).

Evaluation of Palivizumab immunoprophylaxis: 2000-2012

A total of 641 patients were treated with palivizumab between 2000 and 2012 and they were included in this part of the study. Of these, 56 (8.7%) were 24-27 weeks GA; 193 (30.1%) were 28-31 weeks GA; 317 (49.5%) were 32-35 weeks GA and 75 (11.7%) were 36-40 weeks GA. In all, 38.8% (249/641) were under 32 weeks GA and 88.3% (566/641) were ≤35 weeks GA. Mean GA was 32.3 weeks.

Patient characteristics by GA group are shown in Table II. Average birth weight was 1782.6 grams. Of all patients treated with palivizumab, 63 (9.8%) were admitted to the hospital due to a clinical diagnosis of bronchiolitis of any etiology. In 35.5% (22/62) of the samples taken in children admitted due to bronchiolitis were SRV+, therefore only 3.4% of the patients treated with palivizumab presented bronchiolitis with SRV+ (Table III).

TABLE III.—*Bronchiolitis due to SRV+ and SRV- in children treated with palivizumab.*

Gestational age	Bronchiolitis SRV -	Bronchiolitis SRV+
<28	12 (21.4%)	1 (1.8%)
28-31	13 (6.7%)	7 (3.6%)
32-35	29 (9.2%)	12 (3.8%)
36-40	9 (12.0%)	2 (2.7%)
All	63 (9.8%)	22 (3.4%)*

*Three of them did not meet the criteria for having been treated correctly.

The mean age at admission of those admitted due to bronchiolitis was 162 days, while the mean age of those admitted due to SRV+ bronchiolitis was 105 days (P=0.002). The mean length of hospital stay was 8 days in children admitted due to bronchiolitis. Of those, 7.6 days was the mean stay in children who were SRV-, while the mean stay was 9.24 days in SRV+ children (P=0.055). As shown in Table III, the percentage of bronchiolitis SRV- increased in pre-term infants of a younger gestational age.

In addition to being premature, some of the children had additional risk factors: 27/75 (36%) in the 36-40 weeks GA group; 27/317 (8.5%) in the 32-35 weeks GA group; 11/193 (5.7%) in the 28-31 weeks GA group and 8/56 (14.3%) in the 24-27 weeks GA group. Other patients presented conditions deriving from infections: one child of an HIV+ mother, one listeriosis, one adenovirus and one congenital cytomegalovirus. Checked multiple birth in 3.1%.

The patients with an additional risk factor, 13/72 (18%) were admitted due to bronchiolitis compared to 51/558 (9.1%) who did not have additional risk factors (OR=1.99; 95% CI: 0.911-4.044). Of those children with a risk factor in addition to prematurity, 4/13 (30.7%) presented bronchiolitis SRV+, similar to those who did not have additional risk factors (P=0.759). Mean hospital stay in children with an additional risk factor was 8.5 days in children admitted due to bronchiolitis and 9 days for those who had SRV+ (P=0.468).

Comparison between treated and untreated palivizumab groups

Treated patients presented a lower mean birth weight than untreated patients due to their

younger GA (P<0.001). However, when compared according to GA group, no differences observed except in the 32-35 weeks GA group, which presented lower birth weight in the treated patients (P<0.001). Regarding age at admission, the treated children were admitted at an older age than those who were untreated, both in the case of those who were admitted due to bronchiolitis (P<0.001) and those who were admitted due to SRV+ (P=0.042). In terms of length of hospital stay, there was an increase in the treated children compared to the untreated children, both in the case of those who were admitted due to bronchiolitis (P<0.001) and in those who were admitted due to SRV+ (P=0.006).

Discussion

The study performed includes information on hospital admissions for bronchiolitis and children treated with Palivizumab in the 12 years following the authorization of the product. These results are consistent with the available literature. Hospital admission data show a predominance of males (59.5%) compared to females, and a SRV+ percentage of 50-80% among samples taken in children with bronchiolitis, which is similar to other published studies.[3, 4] SRV+ children were also younger on admission than those who were SRV-. This has been previously described, as SRV is associated with bronchiolitis at younger ages, whereas other viruses/agents prevail later on.[9]

It is important to highlight that only 11.5% (98/855) of hospital admissions and 8% (39/488) of SRV+ cases were ≤35 weeks GA. The majority of children who admitted were 36-40 weeks GA (663, 87.1%). Furthermore, age at admission was lower in late pre-term births and term births (118 days in ≥36 weeks GA vs. 158 days in <36 weeks GA, P=0.002), which has been described previously and may be due to greater care in premature infants.[10] Regardless of the fact that age at admission was lower in children ≥36 weeks GA, they had shorter hospital stays (6.8 days in ≥36 weeks GA vs. 7.7 days in <36 weeks GA, P=0.043).

Longer hospital stays are described in previous studies for SRV infections compared to other cases of bronchiolitis.[11] However, in our study we did not observe statistically significant differences in children with bronchiolitis SRV- vs. SRV+ (6.7 vs. 7.06).

Regarding the group of patients previously treated with Palivizumab, is important to highlight that, at our Hospital, this is prescribed according to the SENeo recommendations and 88.3% of children with GA ≤35 weeks are treated.[8] These children presented lower GA than those who had attended the hospital emergency service. Moreover, 11.2% presented additional risk factors that were associated with a greater risk of bronchiolitis VRS-. Nevertheless, the children treated with palivizumab had a higher age at admission. As shown in Tables I and II, we observed in children of 35-40 weeks gestational age increased the days of stay in receiving palivizumab. Previous studies showed that children with similar conditions to those described in the present study, had a higher rate of fever, with a higher temperature and duration. They also required oxygen therapy more often and they remained at the hospital for longer.[12, 13]

Children with underlying diseases and prematurity have high admission rates of up to 13%.[14] In this study, only 22 (3.4%) were admitted due to bronchiolitis caused by SRV. Other observational studies have also found hospitalization rates between 2-4% in premature children and in children with associated conditions treated with Palivizumab.[15, 16]

The efficacy of SRV immunoprevention with Palivizumab has previously reported through prospective and blinded randomized trials such as the Impact study and in patients with heart conditions. Furthermore, in newborns admitted for SRV+ bronchiolitis, the disease had a benign course. To date, studies show that this prevention measure continues to be effective in terms of quality-adjusted life years.[7] The data collected for this study showed low hospitalization rates in premature infants.

Conclusions

In terms of product safety, randomized clinical trials such as the study by Feltes et al.,[17] showed that palivizumab is safe in absolute terms com-

pared to placebo in the short term. Adverse effects after administration were not observed in this study. Nevertheless, prevention through hygiene measures continues to be fundamental in the management of this infection, as suggested by the younger age on admission in late pre-term births. Despite the results of this study and the long series of data available, differences could not be established in the group with underlying conditions due to the low number of cases per condition and the heterogeneous characteristics of each of them. However, an increase in the risk of admission due to non-SRV bronchiolitis could be established in the treated group, showing their vulnerability. Further studies must be conducted to establish immunoprophylaxis recommendations in children with other diseases.[18]

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