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Original Articles

Palivizumab Efficacy in Preterm Infants With Gestational Age ≤30 Weeks Without Bronchopulmonary Dysplasia

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Summary. The present study was designed to determine the efficacy of administration of palivizumab to preterm infants with gestational age (GA) ≤30 weeks without bronchopulmonary dysplasia (BPD). All patients born with GA ≤30 weeks without BPD on Day 28 and hospitalized for RSV bronchiolitis in Burgundy (12 hospitals) from December 1 to April 30 of the next year were included in this prospective observational study during five successive RSV seasons (1999–2000, 2000–2001, 2001–2002, 2002–2003, and 2003–2004). Palivizumab was given to premature infants with a gestational age ≤30 weeks without BPD in the 2002–2003 and 2003–2004 periods only. In the cohort of premature infants with GA ≤30 weeks without BPD, the respiratory syncytial virus (RSV) bronchiolitis hospitalization rate was reduced significantly ($P < 0.01$) in the two seasons with palivizumab prophylaxis (2002–2003: 0% and 2003–2004: 2%) versus the three previous RSV seasons (1999–2000: 14.3%; 2000–2001: 16.7%; 2001–2002: 10.2%). The number needed to treat to prevent one hospitalization for RSV bronchiolitis was 6 (95%CI: 4–11). Such favorable results have not been always found in the few available postmarketing epidemiological studies on hospitalization rate after palivizumab prophylaxis. Differences in health care organization could explain those discrepancies. **Pediatr Pulmonol. 2007; 42:189–192.**

Key words: bronchiolitis; palivizumab; bronchopulmonary dysplasia; pre-term infants; respiratory syncytial virus; prophylaxis.

INTRODUCTION

The safety and efficacy of the passive immunoprophylaxis induced by intramuscular administration of a humanized monoclonal antibody (Palivizumab, Synagis®) was demonstrated in a single randomized, double-blind, placebo-controlled, Phase III trial in which 1,502 premature infants of gestational age (GA) ≤35 weeks with or without

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bronchopulmonary dysplasia (BPD) were included.[1] The overall hospitalization rate for respiratory syncytial virus (RSV) bronchiolitis in those preterm neonates was reduced from 10.6 to 4.8% by palivizumab administration.[1] Following the regulatory approval of palivizumab, epidemiologic studies have reported decreases in RSV bronchiolitis hospitalization rate in groups receiving prophylaxis.[2–7] While those studies came to favorable conclusions with respect to treatment compliance and the safety of prophylaxis, the usual absence of a control group prevented definitive conclusions about the degree of efficacy of palivizumab. Very few studies included a control period and showed discordant results. In a prospective epidemiologic study conducted in Spain, RSV hospitalization rate also markedly decreased from 13.25 to 3.95% in very preterm infants ($\leq$32 weeks post-menstruation) when palivizumab prophylaxis was administered.[8] In France, a regional, prospective, observational study[9] was conducted in Burgundy (population: 1.8 million) over a 3-year period and showed that RSV bronchiolitis hospitalization rate was reduced from 46.2 to 3.8% in very preterm infants with BPD aged less than 6 months at the start of the RSV season. Conversely, a recent study including a control period conducted in the Stockholm area[10] disclosed that the baseline risk of hospitalization was not modified by palivizumab prophylaxis. The authors therefore recommended restricting palivizumab to the small group of very preterm infants suffering from severe chronic lung disease of prematurity (CLD).[10]

So, additional epidemiologic studies with control not prophylaxed periods are necessary and we report herein a French observational region wide study designed to determine the efficacy of administration of palivizumab to premature infants with a GA $\leq$30 weeks without BPD.

MATERIALS AND METHODS

In each of the seasons from December 1 to April 30 of the years 1999–2000, 2000–2001, 2001–2002, 2002–2003, and 2003-2004, all children hospitalized in Burgundy for RSV bronchiolitis were included in this prospective observational study. Bronchiolitis was defined as an acute lower respiratory tract infection occurring during an epidemic season in infants presenting wheezing, retractions, and/or tachypnea.[11] The children were admitted to 12 hospitals (including one teaching hospital with a pediatric intensive care unit) which accept children in the region. For patients with bronchiolitis, the criteria for hospitalization was not pre-defined but left to the attending physician's discretion.

During the five RSV seasons, routine screening for RSV was conducted on nasopharyngeal secretions (using approved enzyme-linked immunosorbent assays or immunofluorescence rapid antigen tests) for all bronchiolitis cases hospitalized in Burgundy. In each hospital, the screening method remained unchanged over the 5 years of the study.

Data was recorded for each child admitted for RSV bronchiolitis and concerned neonatal history characteristics of the episode of bronchiolitis and prior administration of palivizumab.

To obtain a regional uniformity of the practice, the regional network of pediatricians was directly involved in the prospective record of clinical data in patients with RSV bronchiolitis. Validation of recorded data was performed by a research assistant for all patients with RSV bronchiolitis.

According to the Burgundy organization of perinatal care, all patients with GA $\leq$30 weeks, whatever their respiratory status, were initially cared for during the neonatal period in a single regional NICU. Clinical characteristics of the preterm infants with GA $\leq$30 weeks were obtained from the regional perinatal database.[12]

In the 1999–2000, 2000–2001, and 2001–2002 seasons, palivizumab prophylaxis was not given to preterm infants with GA $\leq$30 weeks without BPD according to recommendations from the French health authorities. Seeing high rates of hospitalization for RSV bronchiolitis in these not prophylaxed seasons, the medical board of the Burgundy perinatal network implemented palivizumab prophylaxis for preterm infants with GA $\leq$30 weeks without BPD. In the 2002–2003 and 2003–2004 seasons, on discharge from hospital, palivizumab was administered to preterm infants with GA $\leq$30 weeks without BPD (defined as oxygen-dependence on Day 28 of extra-uterine life) when the following characteristics were met: (a) birth date between April 15 and January 31; (b) less than 6 months old at the start of the RSV season.

Dosage for palivizumab was in agreement with the IMpact-RSV trial.[1]

Statistical Analysis

In the descriptive analysis, the results were expressed as the absolute number and percentage for qualitative variables, and as both mean and standard deviation for quantitative variables.

The tests used in the statistical analysis (SAS 8.2; SAS Institute, Inc.) were Student's *t*-test, the Mann–Whitney test, analysis of variance, and the Kruskall–Wallis test, as appropriate for comparison of means and Pearson's chi^2 test, and Fisher's exact test for comparison of percentages. The significance level was 0.05.

The number of subjects needed to treat (NNT) in order to avoid one RSV bronchiolitis hospitalization was calculated.

RESULTS

As shown in Table 1, the clinical characteristics of preterm infants with GA $\leq$30 weeks born in Burgundy

TABLE 1— Characteristics of the Surviving Preterm Infants With GA ≤30 Weeks Born in the 5 Year Study From April 15 to January 31 and Less Than 6 Months Old at the Start of the RSV Season

	1999–2000	2000–2001	2001–2002	2002–2003	2003–2004
N	47	64	72	75	81
Male/female ratio	59.6%	48.4%	56.9%	56.0%	59.7%
Congenital heart disease	2.1%	1.6%	4.2%	1.3%	4.2%
Birth weight (g)	1153 ± 292	1163 ± 281	1126 ± 293	1158 ± 265	1130 ± 280
GA (weeks)	28.4 ± 1.6	28.5 ± 1.4	28.2 ± 1.5	28.2 ± 1.4	28.5 ± 1.4
RDS	95.7%	93.7%	93.1%	93.3%	89.9%
PDA	31.9%	25.0%	19.4%	24.0%	31.9%
BPD*	57.4%	25.0%	38.9%	49.3%	38.9%

*$P < 0.01$.
BPD, bronchopulmonary dysplasia; RDS, respiratory distress syndrome; PDA, patent ductus arteriosus.

remained unchanged over the five successive seasons except the incidence of BPD (Table 1).

Surviving children born with a GA ≤30 weeks without BPD were 118 in the not prophylaxed periods and 88 in the two prophylaxed periods (Table 2).

In this population of premature infants, the RSV bronchiolitis hospitalization rate was reduced significantly ($P < 0.0001$) in the two seasons with palivizumab prophylaxis (1.1%) as compared with the three not prophylaxed RSV seasons (13.5%), (Table 2). In the last two seasons, palivizumab was administered to 70 of the 88 infants (79.5%) and a single child was hospitalized for RSV bronchiolitis after receiving three injections ofpalivizumab. Palivizumab was not given in 18 infants: 1 because parents refused the prophylaxis; 4 because prophylaxis was inadvertantly missed; 13 because they were born in late January and were discharged from hospital after April 1 at a time when palivizumab prophylaxis was not yet given because of a reduced risk of RSV exposure. The NNT in order to prevent one RSV bronchiolitis hospitalization was 6 [95% CI: 4–11].

DISCUSSION

An important finding in this study was that RSV hospitalization rates in preterm infants with GA ≤30 weeks without BPD were especially high in the not prophylaxed seasons (13.5%). This finding was consistent with that of Carbonell et al.[2,13] who reported an overall hospitalization rate of 13% in comparable infants in Spain.

This observational study demonstrated the efficacy of palivizumab prophylaxis in preterm infants of GA ≤30 weeks without BPD. The RSV bronchiolitis hospitalization rates fell significantly from 14.3, 16.7, and 10.2% in the three seasons without prophylaxis, to 0% and 2% in the two seasons with prophylaxis. Additionally, palivizumab tended to be more effective in preterm infants without BPD, than in infants with BPD as observed in the IMpact study.[1] Indeed, our regional database showed that the NNT in order to avoid one RSV bronchiolitis hospitalization in preterm infants with both GA ≤30 SA and BPD was 13 [95% CI: 4–8]. In these infants with BPD, the RSV hospitalization rate fell from 31% in the not prophylaxed season (1999–2000) to 4.1% in the four following prophylaxed seasons.

It is noteworthy that RSV disease hospitalization rates vary considerably both between and within countries and over time,[2,14–16] as Henckel et al.[10] have stressed. There is a marked between-country variation in the numbers needed to treat (NNT) in order to avoid one hospitalization of RSV disease. Assuming a 55% reduction in the hospitalization rate (the result obtained in the IMpact study[1]), the calculated NNT was 27 in Swedish preterm infants of GA <29 weeks[17] and 43 in Finnish preterm infants of GA ≤32 weeks without CLD[18] Conversely, the NNT was 6 [95% CI: 4–11] in this study. It can be suggested that the type of medical practice (private or public), the socioeconomical level, the rate of breast-feeding, conditions of home care, conditions of health insurance, may greatly influence the rate of bronchiolitis hospitalization.

TABLE 2— Palivizumab Prophylaxis and RSV Bronchiolitis Hospitalization Rates in Preterm Infants With GA ≤30 Weeks Born in the 5 Year Study From April 15 to January 31 and Less Than 6 Months Old at the Start of the RSV Season

	1999–2000	2000–2001	2001–2002	2002–2003	2003–2004
GA ≤30 weeks without BPD (N)	21	48	49	38	50
Palivizumab (N)	0	0	0	29	41
RSV hospitalization (N and %)*	3 (14.3%)	8 (16.7%)	5 (10.2%)	0 (0%)	1 (2%)

*$P < 0.0001$.

Beyond those putative mechanisms, the marked variations in the rate of bronchiolitis hospitalization suggest that interventional epidemiologic studies of RSV respiratory diseases should be conducted at national and/or regional levels in order to implement reliable cost-benefit analyses of palivizumab prophylaxis.

CONCLUSION

Many countries, including France,[3] have adopted restrictive indications for palivizumab prophylaxis in preterm infants because the efficacy of palivizumab is considered limited. The validity of restricting palivizumab indications has not usually been assessed by population-based studies comparing the pre- and post-palivizumab eras. The palivizumab controversy demonstrates that implementation of independent population-based studies will be necessary when new prophylactic agents will obtain regulatory approval and compete with palivizumab.

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