Archives de Pédiatrie xxx (2018) xxx–xxx

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Research paper

Palivizumab administration in preterm infants in France: EPIPAGE-2 cohort study

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ARTICLE INFO

Article history:
Received 17 July 2017
Accepted 14 December 2017
Available online xxx

Keywords:
Bronchopulmonary dysplasia
EPIPAGE-2
Preterm birth
RSV prophylaxis

ABSTRACT

Background: Several countries, including France, have restricted the indications for monoclonal antibodies directed against respiratory syncytial virus (RSV) compared to the marketing authorization (MA). No new data concerning use of palivizumab on a national scale have been published since the 2007 update of the national guidelines.
Objectives: To describe palivizumab administration for RSV prophylaxis during the first RSV season in infants born prematurely in France in 2011.
Methods: Infants from the national population-based cohort EPIPAGE-2 born at ≤ 34 weeks' gestation, discharged home before 31 March 2012 and followed-up at 1 year were included. The RSV season ran from 1 October 2011 to 31 March 2012. Prophylaxis was deemed "initiated" if the infant had received at least one dose of palivizumab during this period and "complete" if it had received at least five doses or as many doses as the number of exposed months. The reference documents were the MA and French Transparency Committee guidelines (TC).
Results: Prophylaxis was indicated in 3586 of 3608 infants (99.7%) according to the MA and 1315 of 3608 (16.7%) according to the TC. A total of 1906 infants (26.6%) received at least one dose of palivizumab. The overall rate of conformity with TC indications was 85%, but was lower for infants born at 27–32 weeks' gestation. The rate of complete prophylaxis was 77.2%. The factors associated with prophylaxis initiation were low gestational age, low birthweight, high maternal educational level, type of neonatal unit, and date at discharge. Factors associated with complete prophylaxis were respiratory impairment, high educational level, and characteristics related to living conditions (absence of siblings at home, type of childcare).
Conclusions: Palivizumab administration in France generally conformed with TC guidelines, but could be further improved for infants born at 27–32 weeks' gestation without bronchopulmonary dysplasia.

1. Introduction

Respiratory syncytial virus (RSV) is the primary cause of lower respiratory tract infections (LRTIs) in infants [1], which may be particularly severe in cases of congenital heart disease or prematurity with bronchopulmonary dysplasia (BPD) [2]. Currently, there are no specific curative treatments or vaccines. Three randomized trials demonstrated that prophylaxis with monoclonal antibodies directed against RSV (palivizumab, Synagis®, AbbVie) led to a 50% reduction in hospitalizations and admissions to intensive care units for RSV-related LRTIs in infants born before 35 weeks' gestation (WG) and under 6 months old at the onset of the RSV epidemic season or below 2 years old and with BPD [3]. These results have been bolstered by several epidemiological studies in Europe and North America [4,5].

Several countries, including France (via the Transparency Committee), have decided upon indications narrower than those of the marketing authorization (MA) [6,7] as a result of the

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https://doi.org/10.1016/j.arcped.2017.12.009
0929-693X/

discussion surrounding cost effectiveness [8]. Indeed, prophylaxis with palivizumab may be cost-effective for only some subgroups of preterm children, but these estimates are difficult to establish [8]. In France, no new data concerning palivizumab use on a national scale have been published since the 2007 update of the Transparency Committee guidelines.

The objectives were to describe practices concerning palivizumab administration during the 1st year of life to infants born before 35 WG in France in 2011, to compare them to the MA and French Transparency Committee indications, and to analyze the factors associated with prophylaxis administration.

2. Materials and methods

2.1. Population

The EPIPAGE-2 study was a prospective population cohort of births between 22 + 0 and 34 + 6 WG conducted in 25 French regions in 2011 [9]. The inclusion period began in March 2011 and lasted 8 months for births at 22–26 WG, 6 months at 27–31 WG, and 5 weeks at 32–34 WG. The initial participation rate was 93%. Information was collected at birth, at discharge from neonatal units, and at corrected ages of 1 and 2 years. The EPIPAGE-2 study was approved by the French Data Protection Authority (CNIL, no. 911009) and ethics committees (CCTIRS 10.626, CPP Île-de-France SC-2873).

This study included EPIPAGE-2 participating infants, alive at 1 year of age and followed up in mainland France. Infants from overseas departments were not included because the start and end dates of the RSV epidemic differ from the mainland. Exclusion criteria were: parental refusal to participate in the 1-year follow-up and a discharge date posterior to 31 March 2012–the end of the RSV epidemic–or unknown. In total, 3608 of 4186 eligible infants (86.2%) were analyzed (Fig. 1).

2.2. Palivizumab administration and indications

Data were obtained by cross-checking the neonatal questionnaires, the parental self-questionnaires at 1 and 2 years and the questionnaire completed by doctors at 2 years.

The RSV seasonal epidemic was from 1 October 2011 to 31 March 2012. Prophylaxis was deemed to have been initiated if the infant had received at least one dose of palivizumab during this period, and complete if it had received at least one dose for each month of RSV exposure in the community, up to five doses. Hence, for complete prophylaxis, infants discharged from hospital before 1 October 2011 had to have received five doses; those discharged during the RSV period had to have received at least as many doses as the number of months between the discharge date and 31 March 2012.

In France, two main documents provide guidelines on palivizumab administration to premature infants [7]. The MA indications (first approval in 1998, indications extended in 2003) are:

- birth $\leq$ 35 WG, age $<$ 6 months at onset of seasonal RSV epidemic;
- age $<$ 24 months at RSV epidemic onset, and BPD requiring treatment in the previous 6 months;
- age $<$ 24 months at RSV epidemic onset and hemodynamically significant congenital heart disease.

The indications of the Transparency Committee, revised in 2007 and laying down the conditions of reimbursement by the French public welfare system, are:

- birth $\leq$ 32 WG, age $<$ 6 months at RSV epidemic onset and respiratory disease ($\geq$ 28 days of oxygen supplementation in the neonatal period);
- birth $\leq$ 32 WG, age $<$ 24 months at RSV epidemic onset, respiratory disease ($\geq$ 28 days of oxygen supplementation), and moderate or severe BPD requiring treatment in the previous 6 months;
- age $<$ 24 months at RSV epidemic onset and hemodynamically significant congenital heart disease.

The Transparency Committee recommends a monthly administration during the RSV exposure period in the community, to be pursued in cases of RSV infection.

2.3. Variable definitions

Birth weight was expressed in percentiles according to French prenatal growth charts accounting for gestational age and sex

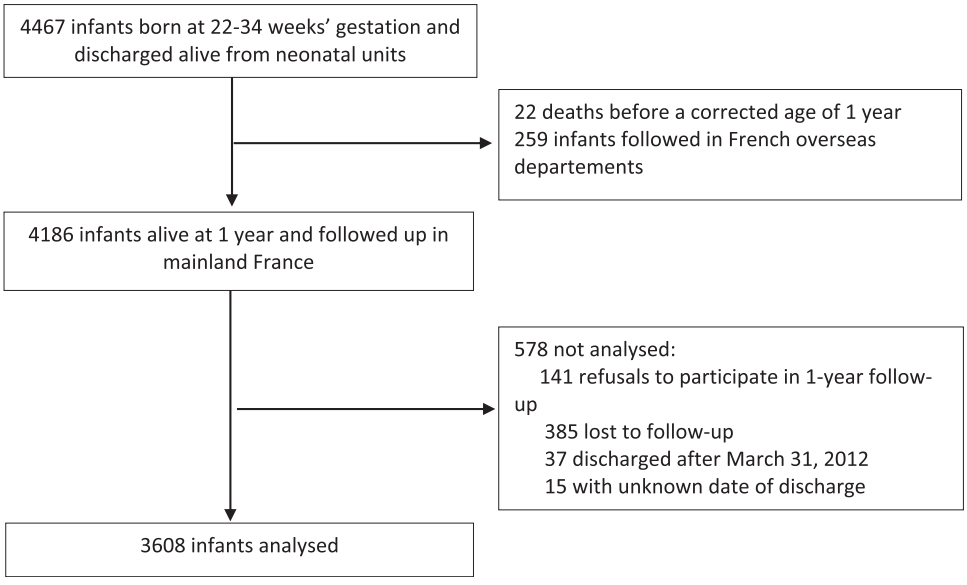

Fig. 1. Flow chart.

Please cite this article in press as: Torchin H, et al. Palivizumab administration in preterm infants in France: EPIPAGE-2 cohort study. Archives de Pédiatrie (2018), https://doi.org/10.1016/j.arcped.2017.12.009