1.0 Abstract

Title: Prospective, Multi-Center, Observational Program to Assess RSV Hospitalization Rate in Population of Children at High-risk of Serious RSV Illness Who Received Palivizumab Immunoprophylaxis in Routine Clinical Setting in the Russian Federation

Keywords: Respiratory syncytial virus (RSV), Lower respiratory tract infections (LRTIs) in children, Humanized IgG1 monoclonal antibody, palivizumab.

Rationale and Background: Respiratory syncytial virus (RSV) is a leading cause of lower respiratory tract infections (LRTIs) in children globally [1, 2, 4]. RSV infection is prevalent in the Russian Federation. In a sample of children aged ≤ 2 years who were hospitalized for LRTI during the RSV season, 38% tested positive for RSV [15]. The prevalence of RSV varied by geographic region and was highest in Moscow (41.7%). The purpose of this post-marketing observational study was to assess the effectiveness of palivizumab in a population of infants and children at high risk of serious RSV disease who received palivizumab in the main regions of Russia.

Palivizumab (a humanized IgG1 monoclonal antibody specific for the F-glycoprotein on the RSV surface) reduces hospitalization from RSV infection in high-risk infants and children [1]. A large (N = 1502), multicenter, randomized Phase 3 trial IMpact-RSV showed that palivizumab prophylaxis reduced RSV-associated hospitalizations in preterm infants and children aged ≤ 24 months with BPD by 55% compared with placebo (4.8% vs. 10.6%, respectively; P = 0.00004). Premature infants without BPD had a 78% reduction in RSV hospitalization (8.1% vs. 1.8%; P < 0.001) whereas children with BPD had a 39% reduction (12.8% vs. 7.9%; P = 0.038 subjects). Similarly, in an international study of children aged ≤ 24 months with hemodynamically significant congenital heart disease (HSCHD; N = 1287), palivizumab prophylaxis resulted in a 45% relative reduction in RSV hospitalizations compared with placebo (5.3% vs. 9.7%, respectively; P = 0.003) [14].

Research Question and Objectives:

Primary Objective:

To assess LRTI hospitalization rate with positive RSV laboratory diagnostic test of respiratory secretions and death due to RSV infection in population of infants at high-risk of serious RSV illness (infants born ≤ 35 weeks of gestation and infants ≤ 24 months with BPD or CHD) who received immunoprophylaxis during the RSV season defined as October 2014 through April 2015 in routine clinical settings in the Russian Federation.

Secondary Objectives:

1. To assess LRTI hospitalization with positive RSV laboratory diagnostic test and Length of Stay (LOS)
2. To assess number of Intensive Care Unit (ICU) admissions within LRTI hospitalization with positive RSV laboratory diagnostic test
3. To assess LOS in ICU within LRTI hospitalization with positive RSV antigen test
4. To assess frequency and duration of supplemental oxygen administration during hospitalization at ICU or hospital ward
5. To assess frequency and duration of mechanical ventilation administration within LRTI hospitalization with positive RSV laboratory diagnostic test
6. To assess compliance to immunoprophylaxis

7. To assess rate of co-morbidities within hospitalizations
Study Design: This was a Phase 4, prospective, multi-center, non-interventional, non-comparative study to access the effectiveness of palivizumab and death due to RSV infection in population of infants at high-risk of serious RSV illness (infants born ≤ 35 weeks of gestation and infants ≤ 24 months with BPD or CHD) who received palivizumab during the RSV season defined as October 2014 through April 2015 in routine clinical settings in the Russian Federation.
Setting: The study took place in 16 clinical sites located in different regions in the Russian Federation.
Enrollment: Subjects were prospectively enrolled in the study from 22 October 2014 until 20 February 2015. Observational visits were scheduled based on routine clinical practice and prescription of palivizumab injection by consulting physician and one follow up visit/termination contact.
Subjects and Study Size, Including Dropouts: Infants at high risk of severe RSV infection receiving palivizumab were identified as candidates for the study on the basis of routine assessments and the parent(s) were asked to provide consent by reading and signing an Informed Consent Form. Patients had to meet all of the following criteria: **Inclusion Criteria:** 1. Planned prescription of palivizumab for immunoprophylaxis during RSV season or patients to whom palivizumab was prescribed and who received the first dose of palivizumab no later than 60 day before enrolment in the study. 2. Infants at high risk of severe RSV infection defined as fulfilling at least one of the following: • Infants born ≤ 35 weeks gestational age AND are ≤ 6 months of age at the onset of the RSV season; • Infants ≤ 24 months of age AND with a diagnosis of BPD (defined as oxygen requirement at a corrected gestational age of 36 weeks); • Infants ≤ 24 months of age with hemodynamically significant CHD, un-operated or partially corrected. 3. Written authorization to use individual data signed by parents or child representative **Exclusion Criteria:** 1. Major congenital malformation aside from CHD. 2. Chronic pulmonary disease other than BPD. 3. Acute period of any infection. 4. Contraindication to palivizumab prescription according to local label. 5. Administration of a product possibly containing RSV-neutralizing antibody within 30 days prior to enrollment or current administration (includes, but is not restricted to, the following: RSV hyperimmunoglobulin, polyclonal intravenous immunoglobulin, cytomegalovirus hyperimmunoglobulin, varicella zoster hyperimmunoglobulin). 6. Previous enrollment in this study.
Statistical Methods: This was an observation study; therefore, the analyses will primarily involve the generation of descriptive summary statistics. The following analysis populations are defined as follows: Safety Analysis Set (SAS) includes all patients who signed patient authorization form to participate in the study and have any collected data. SAS was used for summarizing demographic and baseline characteristics of participants. Full Analysis Set (FAS) included those patients, who signed patient

authorization form, had hospitalization due to LRTI and positive results of RSV laboratory diagnostic test. FAS will be used for analysis of primary and secondary endpoints. Only hospitalizations that occurred while the patient was on scheduled treatment (no delay in more than 10 days in treatment administration) were included for the definition of FAS.

Variables and Data Sources:

Primary variables

Proportion of infants among study population who were

- hospitalized for LRTI and the RSV laboratory diagnostic test of respiratory secretions was positive
- or died as caused by RSV and diagnosis confirmed by autopsy or clinical history and virologic evidence.

Secondary variables

1. Median LOS of LRTI hospitalization with positive RSV laboratory diagnostic test (days)
2. Proportion of patients with ICU admission among hospitalized patients
3. Median LOS in ICU (days)
4. Proportion of patients who received supplemental oxygen within hospitalization and median duration of oxygen administration at ICU or hospital ward (days)
5. Proportion of patients who received mechanical ventilation and median duration of mechanical ventilation administration at ICU (days)
6. Proportion of patients missed 1 dose, 2 doses, ≥ 3 doses
7. Proportion of patients with all co-morbidities within hospitalization and proportion of patients with particular co-morbidity defined with ICD-10

Data Sources

Data for the study were collected within clinical interview with parents or care giver/representative of the child and from source document at the center. Source documents were original documents, data and records. This might include hospital records, clinical and office charts, laboratory data/information or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, etc.

The RSV laboratory diagnostic test was not specified by protocol. Test results were obtained from hospital records.

Results

- Starting on 22 October 2014 and ending on 20 February 2015, a total of 359 patients were enrolled in the study at 16 clinical sites in the Russian Federation.
- Overall, 86.9% (n = 312) of children received three or more planned injections of palivizumab 22.6% (n = 81) of children missed or had a delayed palivizumab injection of at least 10 days. Forty-two percent (n = 153) of patients completed the study.
- The median chronological age of infants enrolled in the study was 2.0 months, ranging from 0 to 21.0 months, 50.1% (n = 180) were male. 41% (n = 148) were children ≤ 24 months of age with a diagnosis of BPD, and 13% (n = 45) were children ≤ 24 months at enrollment with HSCHD.
- In total, 12 hospitalizations due to LRTI were reported during the study among 11 patients (3.1%; 95% CI 1.5, 5.4).

- A RSV diagnostic test was performed in 9 of the 11 cases of LRTI hospitalization. Subsequently, one case of RSV positive LRTI was detected, resulting in a RSV LRTI hospitalization rate of 0.3% (1/359). The infant hospitalized for RSV positive LRTI was born prematurely (27 weeks gestational age) and was diagnosed with bronchopulmonary dysplasia. The patient received 3 injections of palivizumab, the last injection was received 15 days before hospitalization. Duration of RSV-positive hospitalization for this patient was 46 days, which included 35 days in the ICU. Supplemental oxygen therapy was administered for 30 days, mechanical ventilation was not performed. RSV-positive pneumonia resolved in this patient.
- Forty-one treatment emergent adverse events (AEs) were reported in 19 of 359 (5.3%) subjects through 30 days following the last observation visit. No AE led to discontinuation of palivizumab. There were no AEs that exceeded a 5 % frequency threshold. The most common AE was viral respiratory tract infection with a rate of 1.9% (n = 7) followed by bronchitis (1.4%, n = 5) and pneumonia (1.4%, n = 5).
- Nine AEs in 3 subjects (0.8%) were assessed as possibly related to palivizumab and included bronchopneumonia, pneumonia, viral respiratory tract infection, apnoea, BPD, dyspnea, cough, decreased appetite and lethargy.
- Thirty-three serious adverse events (SAEs) were reported among 17 (4.7%) subjects through 30 days following the last observation visit. The most frequent SAE were pneumonia (7 or 2.0% of patients), viral respiratory tract infection (6 or 1.7% of patients) and bronchitis (5 or 1.4% of patients). 4 (1.1%) patients with combined pathology died during the study, two of them had pneumonia. No cases of death due to RSV infection were reported in this study.

Discussion

This study provides the first demonstration of the real world effectiveness of palivizumab in a population of infants at high risk of serious RSV illness in routine clinical settings in the Russian Federation.

The LRTI hospitalization rate was low; overall 12 LRTI-hospitalizations were reported in 11/359 (3.1%) infants (95% CI 1.5% – 5.4%).

A RSV diagnostic test was performed in 9 of the 11 cases of LRTI hospitalization, subsequently one case of RSV positive LRTI was detected, resulting in a RSV hospitalization rate of 0.3% (1/359). Of note, a rapid antigen test was used in 8 of the 9 cases tested for RSV. Palivizumab may interfere with immune-based RSV diagnostic tests, such as some antigen detection-based assays, which could result in false negative results.

Compliance to immunoprophylaxis with palivizumab was evaluated in this observational study (secondary objective). This "real-world" study reported relatively high non-compliance with optimal schedule of immunoprophylaxis with palivizumab: 22.6% of infants received at least one palivizumab injection after incorrect dose timing (missed or delayed for more than 10 days injection). Also more than half of patients (57.4%) were discontinued immunoprophylaxis with palivizumab prematurely, the main reason of early discontinuation was related to administrative problems, namely the lack of study drug.

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decreased appetite and lethargy. Thirty-three serious adverse events (SAEs) were reported among 17 (4.7%) subjects through 30 days following the last observation visit. The most frequent SAE were pneumonia (7 or 2.0% of patients), viral respiratory tract infection (6 or 1.7% of patients) and bronchitis (5 or 1.4% of patients). 4 (1.1%) patients with combined pathology died during the study, two of them had pneumonia. No cases of death due to RSV infection were reported in this study.
Conclusions: – The observational study met its main objectives to assess the effectiveness of palivizumab and death due to RSV infection in a population of infants at high risk of serious RSV illness (infants born ≤ 35 wGA and infants ≤ 24 months with BPD or CHD) who received palivizumab prophylaxis during the RSV season 2014 – 2015 in routine clinical setting in the Russian Federation. – Palivizumab was effective as demonstrated by one confirmed RSV LRTI hospitalization among 359 patients observed (0.3%). The low rate of RSV hospitalization observed in this study is consistent with the hospitalization rates of 4,8% and 5.3% reported in the palivizumab pivotal studies among children randomized to palivizuamb (1, 14). – In addition, palivizumab was well-tolerated in this mixed population of patients at high risk for serious RSV infection. The overall safety data is consistent with the safety profile in the indicated populations established during the clinical development of palivizumab and through 15 years of global post-marketing use as summarized in the product label. – Thus, the effectiveness and safety of palivizumab was confirmed in a small mixed population of Russian patients at risk for serious RSV infection and the benefit-risk profile observed in this study is consistent with the established benefit risk profile.

Marketing Authorisation Holder(s)

AbbVie LLC, Russia

[redacted]

Names and Affiliations of Principal Investigators

The study was conducted in 16 clinical centers located in different regions of Russia. All personnel involved at the clinical site were qualified to perform their roles. The full list of the investigators with their positions and contact details is provided in [redacted]