1.0 Abstract

Title

Synagis® liquid 50 mg, 100 mg for Intramuscular Injection: Special Investigation in Immunocompromised Children with Synagis®

Keywords

Palivizumab, respiratory syncytial virus, immunocompromised children, Down syndrome

Rationale and Background

The Japanese Ministry of Health, Labour and Welfare (MHLW) requested the clinical development of palivizumab for prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (hereinafter referred to as "RSV") infection in immunocompromised newborns, infants, and young children aged 24 months or younger who have received organ transplants, undergone bone marrow transplantation, or are on chemotherapy in accordance with the "Request for Clinical Development of Unapproved and Off-label Drugs" (HPB/RDD Notification No. 1213-1 and PFSB/ELD Notification No. 1213-1) dated December 13, 2010. As a result, Study M12-420 was conducted beginning August 2011, ending on April 2012. This was a multi-center, open-label, multiple dose, uncontrolled clinical study (ClinicalTrials.gov Identifier: NCT01466062) of palivizumab in Japanese newborns, infants and young children at the age of 24 months or less with immunocompromised medical conditions including children diagnosed with Down syndrome without a current hemodynamically significant congenital heart disease (hs-CHD). This study was conducted in 28 subjects. On the basis of these data, 2 new indications were granted for palivizumab in 2012 for the prevention of serious lower respiratory tract disease caused by RSV infection in newborn, or infants, or young children, at the early phase of RSV infection season:

- Newborns, or infants, or young children, at the age of 24 months and under, who have immunocompromised medical condition.
- Newborns, or infants, or young children, at the age of 24 months and under, who have Down syndrome.

As a post-authorisation commitment, the Japanese MHLW requested a post-marketing observational study of palivizumab to be performed for the purpose of obtaining safety and effectiveness data in patients with a compromised immune system including Down syndrome. As a result, AbbVie conducted Study P14-296 (Synagis® Liquid 50 mg, 100 mg for intramuscular injection, special investigation in immunocompromised children with Synagis®). This study was conducted in newborns, or infants, or young children at the age of 24 months and under, who have an immunocompromised medical condition including children diagnosed with Down syndrome without a current hs-CHD.

Research Questions and Objectives

To assess the safety and effectiveness of palivizumab in newborns, infants and young children ≦ 24 months of age with immunodeficiency and Down syndrome who received palivizumab for prevention of serious lower respiratory tract disease caused by RSV infection during the 2013-2014 and 2014-2015 RSV seasons in routine clinical settings in Japan.

Research Methods

Study Design

This was a multi-center, non-interventional, non-comparative, prospective cohort study (Post- Marketing Observational Study) to assess the safety and effectiveness of palivizumab in children with immunocompromised conditions or Down syndrome during the 2013-2014 and 2014-2015 RSV seasons in routine clinical settings in Japan.

Setting

The study took place in 63 clinical sites located in different regions in Japan.

The research sites included medical centers/institutions with access to this patient population and have the ability to appropriately conduct the prospective, observational, non-interventional study in accordance with applicable legal and regulatory requirements. A written agreement was concluded between AbbVie and each participating institution.

Enrollment

Subjects were prospectively enrolled in the study from 19 December 2013 until 03 December 2015 after obtaining informed consent to participate in this study from subject's parents or legal guardian. Observational visits were scheduled based on routine clinical practice and prescription of palivizumab injection by consulting physician.

The observation period was from the first palivizumab injection to 30 days after the final injection, including when palivizumab was discontinued prematurely.

Subjects and Study Size, Including Dropouts

Japanese subjects who met all of the inclusion criteria and none of the exclusion criteria were eligible for study participation.

The study employed the consecutive enrollment method to reduce possible selection bias.

Inclusion Criteria

Availability of parent or legal guardian who was capable and willing to give written informed consent for his/her newborn, infant or young child to participate in this study.

Patients receiving palivizumab for prevention of serious lower respiratory tract disease caused by RSV infection

- Newborns, or infants, or young children, at the age of 24 months and under, who have immunocompromised medical conditions including:
  - combined immunodeficiency, (severe combined immunodeficiency, X-linked hyper-immunoglobulin M (IgM) syndrome, etc.), antibody deficiency (X-linked agammaglobulinemia, common variable immunodeficiency, non-X-linked hyper-IgM syndrome, etc.) or other immunodeficiency (Wiskott-Aldrich syndrome, etc.)
  - acquired T cell dysfunction (such as human immunodeficiency virus (HIV) infection etc.)
  - history of post organ transplantation
  - history of post bone marrow transplantation
  - receiving immunosuppressive chemotherapy
  - receiving systemic high-dose corticosteroid therapy (prednisone equivalents ≥ 0.5 mg/kg/every other day, other than inhaler or topical use), or
  - receiving other immunosuppressive therapy (azathioprine, methotrexate, mizoribine, mycophenolate mofetil, cyclophosphamide, cyclosporine, tacrolimus, cytokine inhibitors, etc.)
  - receiving biologics (including cytokine inhibitors)
  - Others (nephrotic syndrome, chronic peritoneal dialysis, hemodialysis)
- Newborns, or infants, or young children, at the age of 24 months and under, who have Down syndrome without current hs-CHD. The subject must have had an experience with persistent respiratory symptoms or regular outpatient treatment due to respiratory tract infection prior to current RSV season.

Exclusion Criteria

Patients included in "Contraindication" in the package insert, and patients with the following exclusion criteria:

- Patients with known hypersensitivity to the ingredients of palivizumab
- Patients with known positive RSV infection before hospitalization

Patient and Clinical Variables Collected

Patient characteristics, RSV testing, hospitalization, oxygen inhalation or artificial respiratory support, palivizumab administration, concomitant drug use, and adverse events (AE). Lower Respiratory Tract Infection (LRI) Score: 0: Well or baseline, 1: Upper Respiratory tract Infection (URI) mild, 2: LRI, 3: Moderate LRI, 4: Severe LRI, 5: Respiratory Failure. Clinical condition and respiratory component score (0-5) based on respiratory rate per minute, oxygen saturation, and physical findings.

Data Sources

Data for the study were collected from source documents at the institutions. 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 tests specified by protocol included antigen test, antibody test [complement fixation test, neutralization test], culture, and PCR. Test results were obtained from hospital records.

Study Size

Number of the sample size: 250 patients / 2 RSV seasons

Data Analysis

This was an observational study; therefore, the analyses will primarily involve the generation of descriptive summary statistics. The Case Report Form (CRF) was used for summarizing demographic and baseline characteristics of participants. The analysis populations are defined as follows: safety analysis set includes patients enrolled per protocol using consecutive enrollment method, had completed CRF and

did not have any of the following: 1) enrollment at any non-contracting institution/department or beyond the contracted number 2) duplicate enrollment 3) no palivizumab administration 4) began palivizumab administration out of the investigation period. The effectiveness analysis includes those patients included in the safety analysis set who also meet study eligibility criteria.

Multivariate logistic regression analysis was used to identify demographic and baseline variables that could significantly affect the risk of AEs and Adverse Drug Reactions (ADR)s.

Rationale for Setting

Incidence of ADRs

Data was to be collected from 125 patients per year (season) for 2 years (seasons) to supplement the limited amount of data collected in clinical Study M12-420. With data from 250 patients and an incidence rate of ADRs of 1.2%, the probability that one or more ADRs are reported is at least 95%. Of the AEs reported in the Study M12-420 with "possible" or "probable" assessment for their relationships to palivizumab, the incidence of "conjunctivitis (eye disorders)" and "encephalopathy (nervous system disorders)" was both 3.6% (1/28 each).

Results

Starting on 19 December 2013 and ending on 03 December 2015, a total of 312 patients were enrolled in the study at 63 clinical sites in Japan.

The safety analysis set consisted of 304 patients. The patients excluded from safety analyses were as follows: patients who violated the consecutive enrollment method (2 patients); duplication enrollment (2 patients); patients who started administration outside of the investigation period (2 patients); and patients who did not meet eligibility criteria for the investigation (2 patients). The effectiveness analysis set consisted of 288 patients. The patients excluded from effectiveness analyses were as

follows: 8 patients excluded from the safety analysis set, 13 patients that did not meet the inclusion criteria, i.e., one patient diagnosed with Down syndrome without a current hs-CHD and no experience with persistent respiratory symptoms or regular outpatient treatment due to respiratory tract infection prior to current RSV season, and 3 patients who were in hospital for RSV infection at the start of palivizumab administration.

Of the patients, 61.5% (187/304) were male and 97.7% (297/304) were Japanese. The mean ± standard deviation (SD) of age in months was 11.9 ± 7.5 months, and the mean ± SD of body weight was 7493.2 ± 2486.3 g. The mean ± SD of gestational age in weeks was 37.8 ± 2.0 weeks, and the mean ± SD of body weight at birth was 2777.1 ± 513.5 g.

The reasons for palivizumab administration reported by the investigator were immunocompromised conditions in 54.9% (167/304) of patients and Down syndrome in 45.4% (138/304) of patients. One patient had an immunocompromised condition and Down syndrome. Immunocompromised conditions (one subject may be counted more than once) included primary immunodeficiency syndrome with abnormal T cell function (16 patients), acquired T cell dysfunction (such as HIV infection, etc.) (1 patient), solid organ transplantation (33 patients), hematopoietic stem cell allograft (25 patients), autologous hematopoietic stem cell transplantation (3 patients), myelosuppressive chemotherapy (68 patients), bone marrow failure (e.g., aplastic anemia) (3 patients), high-dose adrenocortical steroid therapy (15 patients), immunosuppressive therapy (21 patients), and use of biologics (2 patients). Other indications were congenital nephrotic syndrome (5 patients) and use of chronic peritoneal dialysis/hemodialysis (16 patients).

The mean ± SD of the number of palivizumab doses during the RSV season was 5.3 ± 2.4 doses, with a minimum of 1 and a maximum of 10. The mean ± SD dose per body weight was 14.87 ± 1.08 mg/kg, and the mean ± SD dose interval was 31.4 ± 7.4 days. The status of final administration is as follows, 85.5% (260/304) completed administration with palivizumab and 14.5% (44/304) discontinued

administration. Seven children discontinued palivizumab due to an AE. Administration discontinuation was mainly due to failure to show up/transfer to another hospital, which was reported in 8.2% (25/304) of the patients.

Safety

A total of 220 AEs were reported in 99 patients in the investigation, with an incidence of 32.57% (99/304). The most frequently reported AEs were upper respiratory tract inflammation with a rate of 7.57% (23 events), followed by febrile neutropenia with a rate of 3.62% (11 events), and followed by pneumonia with a rate of 2.30% (7 events). Of the AEs reported, 89 events in 53 patients were considered SAEs, with an incidence of SAEs of 17.43% (53/304).

The most frequently reported SAE was pneumonia with a rate of 1.97% (6 events). Of the SAEs reported, 8 events in 6 patients were assessed as "fatal" for their outcome. These 8 events included sepsis (1 event), septic shock (1 event), bacteremia (1 event), malignant neoplasm progression (1 event), cardiac failure (1 event), hepatic failure (1 event), respiratory failure (1 event), and brain neoplasm malignant (1 event). Of the 8 events, 7 were not considered treatment-related. One fatal event of septic shock in 1 patient was considered by the investigator as an adverse drug reaction but the causality to study drug was stated as not assessable.

Multiple logistic regression analysis with the presence/absence of AEs as dependent variable was performed to identify the factors that may affect AEs. The following factors were associated with the presence/absence of AEs (Odds ratio; 95% CI), presence of a comorbidity (3.263; 1.612, 6.605), presence of a comorbidity: Cardiovascular disease (0.371; 0.147, 0.937), reason for prophylactic administration: Solid organ transplantation (0.111; 0.031, 0.395); prior medication: adrenocortical steroids (0.248; 0.088, 0.703); concomitant drug: adrenocortical steroids (4.296; 1.652, 11.171) and concomitant drugs: others (31.436; 3.893, 253.843).

A total of 33 ADRs were reported in 25 of the 304 patients in the safety analysis set, with an incidence of 8.22% (25/304). Of the ADRs reported, 13 events in 11 patients were considered a serious ADR, with an incidence of serious ADRs of 3.62% (11/304).

The most frequently reported ADRs were upper respiratory tract infection with a rate of 1.64% (5 events), followed by pneumonia with a rate of 0.99% (3 events) and RSV infection with a rate of 0.99% (3 events).

Of the serious ADRs reported, 5 events were considered unexpected according to the current Japan Package Insert: septic shock, device related infection, nephroblastoma, asthma, and drug-induced liver injury. The event of drug-induced liver injury was reported in a patient approximately 1 month after the first dose of palivizumab administration. The investigator considered that the causality to palivizumab for this liver event could not be rule out. The outcome of the 13 serious ADRs included 6 events of recovery, 5 events of remission, 1 event of not recovered (nephroblastoma), and 1 event of fatality (septic shock). Table 10-10 provides further information regarding the reported SADR that was assessed as "fatal" for its outcome.

Multiple logistic regression analysis with the presence/absence of ADRs as dependent variable was performed to identify the factors that may affect ADRs. The following factors were associated with the presence of ADRs (Odds ratio; 95% CI); the existence of a comorbidity: others (5.47; 1.75, 17.14), and concomitant drug: biologics (13.911; 1.103, 175.401).

Effectiveness

Of the 288 patients in the effectiveness analysis set, 5 (1.7%) had an RSV infection during the investigation period, including 2 patients who required hospitalization. The rate of hospitalization due to RSV infection was 0.7% (2/288). The mean ± SD of the number of days of hospitalization was 9.5 ± 2.1 days. The two subjects were male, 40 weeks and 37 weeks gestational age, respectively, and were administered

palivizumab for the indication of Down syndrome, with no congenital heart disease. The mean ± SD of LRI score was changed between 0.0 ± 0.0 from 0.1 ± 0.6 during the administration of palibizumab.

Discussion

This investigation was conducted as a post-marketing surveillance study of palivizumab from December 2013 to December 2015. A total of 304 patients were included in the safety analysis set and 288 patients in the effectiveness analysis set.

The indications of palivizumab reported in the investigation were immunocompromised conditions in 54.9% (167/304) of patients and Down syndrome in 45.4% (138/304) of patients.

A total of 220 AEs were reported in 99 patients in the investigation, with an incidence of 32.57% (99/304). The most frequently reported AEs were upper respiratory tract inflammation with a rate of 7.57% (23 events), followed by febrile neutropenia with a rate of 3.62% (11 events), and followed by pneumonia with a rate of 2.30% (7 events). Of the AEs reported, 89 events in 53 patients were considered SAEs, with an incidence of SAEs of 17.43% (53/304). In the Study M12-420, a total of 27 AEs were reported, with incidence of 96.4% (27/28), and of the AEs reported, 7 events were considered a SAEs, with incidence of SAEs of 25.0% (7/28).

A total of 33 ADRs were reported in 25 of the 304 patients in the safety analysis set, with an incidence of 8.22%. Of the ADRs, 13 events in 11 patients were considered a serious ADR, with an incidence of serious ADRs of 3.62% which was not higher than what was observed in the Study M12-420, with the incidence of ADRs 25.0% (7/28).

Of the 288 patients in the effectiveness analysis set, 5 had RSV infection during the investigation period, including 2 patients who required hospitalization. The rate of hospitalization due to RSV infection was 0.7% (2/288). The rate of hospitalization due to RSV infection in Study M12-420 was 0.00% (0/28), although the rates cannot be directly compared to each other.

The review of the safety data from the current study did not identify any new safety signals or concerns. Although there was no placebo / control group to definitely claim, AEs reported were typical of a pediatric study population, and in a population with immunocompromised children.

The benefit-risk profile of palivizumab remains favorable for the approved indications in Japan; therefore, this investigation supports the safety and effectiveness in the clinical setting of palivizumab used in immunocompromised newborns, infants, and young children up to the age of 24 month and newborns, infants, and young children up to the age of 24 months who have Down syndrome during the RSV infection season. The results of the investigation support what was observed in Study M12-420 which was the basis for the approval of the new indication.

The study population was a very specific, defined population, observed in the context of daily practice; therefore, the results of this study may not be applicable to the general population of healthy infants in Japan.

Marketing Authorization Holder(s)

AbbVie GK

[redacted]

Names and Affiliations of Principal Investigators

Not applicable.