Eur J Clin Microbiol Infect Dis (2003) 22:414–417
DOI 10.1007/s10096-003-0961-z

ARTICLE

J. R. Groothuis

Safety of Palivizumab in Preterm Infants 29 to 32 Weeks' Gestational Age Without Chronic Lung Disease to Prevent Serious Respiratory Syncytial Virus Infection

Published online: 24 June 2003
© Springer-Verlag 2003

Abstract Respiratory syncytial virus is an important cause of hospitalization in preterm infants. Palivizumab, a humanized monoclonal antibody against the respiratory syncytial virus fusion protein, is currently the only licensed product in Europe available for prophylaxis of respiratory syncytial virus lower respiratory tract infection. This study was conducted to obtain additional European data on the safety of palivizumab in preterm infants 29–32 weeks' gestational age without chronic lung disease. Subjects less than 6 months old were enrolled between October 2000 and April 2001. Demographic information was obtained and physical examination was performed at enrollment. Subjects received 15 mg/kg palivizumab intramuscularly every 30 days for the duration of the respiratory syncytial virus season. Subjects hospitalized for respiratory illness were tested for respiratory syncytial virus infection with respiratory syncytial virus rapid antigen tests. At monthly visits, interim history for adverse events/respiratory illness and physical exam was performed. A total of 285 subjects were enrolled from 35 centers in 18 countries. The mean (±SD) gestational age was 30.8±1.1 weeks, the mean birth weight 1.5±0.4 kg, and 56% were <12 weeks of age at enrollment. Over 80% of patients received at least four palivizumab doses; all received at least one dose. The most commonly reported adverse events (>5%) were rhinitis, increased cough, fever, pharyngitis, bronchiolitis, and diarrhea. Only six subjects reported adverse events that were considered possibly related to palivizumab. No deaths were reported. Twenty subjects were hospitalized during the study; six of these were respiratory syncytial virus positive. Palivizumab is safe and well tolerated in preterm infants 29–32 weeks' gestation without chronic lung disease.

J. R. Groothuis (✉)
Department R438, Building AP30-2,
Abbott Laboratories,
200 Abbott Park Road, Abbott Park, IL 60064-6149, USA
e-mail: Jessie.Groothuis@abbott.com
Tel.: +1-847-9359526
Fax: +1-847-9365845

Introduction

Respiratory syncytial virus (RSV) is a primary cause of viral respiratory illness requiring hospitalization in infants and children worldwide and occurs in annual, seasonal epidemics. The peak incidence of RSV infection occurs between 2 and 6 months of age, with half of all infants becoming infected in the first year of life [1, 2].

RSV is particularly threatening in preterm infants because of underlying anatomic and immunologic risk factors. Infants born at 29 to 32 weeks' gestational age (wGA) have smaller airways and poorly developed lungs compared to full-term infants [3, 4]. Substantial pulmonary development occurs in the final stages of pregnancy (30 wGA to term). Lung volume also increases markedly in the last trimester from 25 ml to 150–200 ml. The same is true of alveolar diameter, which increases from 32 μm to 150 μm.

Preterm infants also have significantly lower serum IgG immunoglobulin levels during the first several months of extra-uterine life [5]. RSV IgG antibody is essential to protect the lower airways from RSV infection. IgG is transferred from the mother to the fetus only in the last trimester of pregnancy, and RSV IgG has been shown to be low or absent in preterm infants less than 32 wGA [6, 7].

Prevention of serious RSV disease in general has been problematic, and the inability to develop safe and effective RSV vaccines stems from several factors [2, 8, 9, 10, 11]. Palivizumab, a humanized monoclonal antibody specific for the RSV F (fusion) protein, is currently the only approved pharmaceutical agent available in Europe for passive prophylaxis against RSV lower respiratory tract infection. The IMpact-RSV phase III trial that resulted in EMEA (the European agency for the evaluation of medical products) approval evaluated the safety and effectiveness of monthly administration of palivizumab as prophylaxis for serious RSV illness in preterm (≤35 wGA) infants and children [12]. The results showed that monthly intramuscular injections of 15 mg/kg palivizumab during the RSV season reduced the

incidence of RSV-related hospitalization by 55%. This study established palivizumab as safe and effective for prevention of serious RSV illness in premature infants with and without chronic lung disease.

Infants born at 29 to 32 wGA without chronic lung disease were not included as a specific subset of the patients evaluated in the IMpact-RSV study, and palivizumab safety has not been widely studied clinically outside of the USA and North America in this population. Therefore, we conducted the PROTECT (Palivizumab RSV Open-label Trial of Effectiveness and Clinical Tolerability) study in 17 European countries and Saudi Arabia. This was a prospective phase IV study to obtain additional data on the safety and tolerability of palivizumab in preterm infants between 29 and 32 wGA who were less than 6 months of age without chronic lung disease.

Materials and Methods

We conducted the PROTECT study in infants born between 29 and 32 wGA and who were less than 6 months of age and without chronic lung disease at the onset of the RSV respiratory season. The primary objective was to assess the safety of palivizumab in this population and compare it with that observed in the IMpact-RSV Trial [12]. The incidence of RSV disease severity as defined by need for hospitalization and hospital course was also assessed. Exclusion criteria included hospitalization or mechanical ventilation (including continuous positive airway pressure) at the time of enrollment (excluding hospitalization from birth), a diagnosis of chronic lung disease, active illness/infection (including RSV) at the time of enrollment, known renal impairment or hepatic dysfunction, chronic seizure disorder, congenital heart disease, known immunodeficiency, previous treatment/prophylaxis with monoclonal antibodies other than palivizumab, or life expectancy less than 6 months.

We obtained a medical history and performed a physical examination on all study subjects prior to the first palivizumab injection. Subjects were enrolled according to procedures consistent with local regulatory requirements in their respective countries. Informed consent from the parent or guardian was obtained for all subjects. An independent ethics committee that complied with each country's regulatory requirements reviewed and approved the protocol, amendments, informed consent form, and all other forms of subject information related to the study. The study was conducted in accordance with the Declaration of Helsinki and its revisions [13].

Study infants were enrolled to assure that the majority of subjects would receive their first palivizumab injection prior to the onset of the RSV season. The study was therefore conducted from October through April to accommodate length and variation in RSV epidemics across the different countries participating in the trial. On the first day of enrollment into the study, palivizumab was administered 15 mg/kg intramuscularly in the anterolateral area of the thigh as per standard pediatric nursing practice. The study drug dose was calculated based on the child's current weight (to the nearest 0.01 kg) using the following formula: dose (ml) = [patient weight (kg) × 15 mg/kg] ÷ study drug concentration (100 mg/ml). Injection volumes over 1 ml were to be given as a divided dose. The injections were administered approximately every 30 days for the duration of the RSV season (winter through early spring). Vital signs were assessed immediately prior to as well as 30 min after each injection. Subjects remained in the office for observation during the 30-min postinjection period.

Subjects' parents were instructed to report any abnormalities to study personnel between study visits over the telephone and to bring the child to the study site if medical evaluation was necessary (as medical urgency allowed). Additionally, at each monthly visit, subjects were monitored for clinical and laboratory evidence of adverse events. Physical exams (vital signs, weight, respiratory rate, chest exam) were performed. Medical records were confirmed for all unscheduled visits to clinics or emergency facilities. Subject monitoring for adverse events continued for 30 days following the final palivizumab injection.

Study physicians defined the criteria for hospitalization for respiratory illnesses. All sites were supplied with Abbott Testpack RSV kits (Abbott, USA). The reported sensitivity of this kit is 94.3%, and the specificity is 95.3% (Abbott Testpack RSV Immediate Care Diagnostics, package insert, June 2000). Subjects hospitalized for respiratory illnesses or infections were evaluated for RSV infection by RSV rapid antigen detection in respiratory secretions. Infants hospitalized for lower respiratory tract illness were monitored for total days of hospitalization and need for intensive care unit stay, supplemental oxygen, or mechanical ventilation. We continued to monitor hospitalized patients for adverse events according to the protocol, and patients continued to receive monthly palivizumab injections according to schedule.

Statistical Analysis

This was an "intent-to-treat" study; therefore all patients who received at least one palivizumab injection were included in the statistical analysis. Baseline characteristics were summarized using mean, standard deviation, median, range for continuous variables, and frequency and percentage for categorical variables. Outcomes data were summarized.

Safety Analysis

Adverse events were summarized by body system, COSTART V (Coding Symbols for Thesaurus of Adverse Reaction Terms, Dictionary Version 5) term, severity, and relatedness to study drug. Listings of serious adverse events reported during the study and their relatedness to study drug were provided. Serious adverse events were defined as any adverse event that resulted in death, life-threatening situation, inpatient hospitalization, persistent or significant disability or incapacity, congenital anomaly or birth defect, or other medically important events.

Results

A total of 285 subjects were enrolled in the study at 35 centers from 17 European countries and Saudi Arabia during the 2000–01 respiratory season. This study was designed as "intent-to-treat," and all 285 subjects were included in the final analysis. All 285 subjects received at least one palivizumab injection, and 83% received four or five doses. No deaths were reported.

Demographic characteristics for the study population are presented in Table 1. Twenty-four of the 285 subjects did not complete the study: 12 withdrew consent, two discontinued due to adverse events, five were lost to follow-up, and five withdrew for other reasons. The two patients who discontinued for adverse events did so for the following reasons: the first patient had a gastrointestinal disorder with peripheral edema and apnea of moderate severity not related to the study drug; the second patient experienced high fever lasting 15 h after receiving her third dose of palivizumab. The episode was considered to be moderately severe and to be probably related to the study drug.

Table 1 Demographic characteristics of the 285 subjects at enrollment

Characteristic	
Gestational age in weeks (mean±SD)	30.8±1.1
Birth weight in kg (mean±SD)	1.51±0.37
Age (weeks) at enrollment (mean±SD)	12.1±7.3
<12 weeks	160 (56%)
±12 weeks	125 (44%)
Sex	
Male	151 (53%)
Female	134 (47%)
Race	
Caucasian	257 (90%)
African	2 (1%)
Asian/Pacific Islander	10 (4%)
Mixed	1 (0.4%)
Other	15 (5%)

The most commonly reported adverse events (reported by >5% of subjects) were rhinitis (18%), increased cough (10%), fever (7%), and diarrhea, bronchiolitis, and pharyngitis (each 5%). The majority of reported adverse events were mild to moderate in severity. The adverse events that were considered by the investigator possibly or probably related to palivizumab and their severity classification are summarized in Table 2.

Twenty subjects were hospitalized for respiratory-related infections during the study (3 subjects were hospitalized twice). Six subjects who were hospitalized were RSV positive and 17 were RSV negative. Two of the RSV-positive subjects were hospitalized twice, but RSV was not the cause in the second hospitalization. One of the RSV-positive subjects was hospitalized for an upper respiratory infection, while the other five had lower respiratory tract infection, resulting in an incidence of RSV lower respiratory tract infection-related hospitalization of 1.8%. A large number of study infants had epidemiological and demographic factors known to predispose them to greater risk for hospitalization caused by RSV [2]. Such factors included multiple birth status (28% twin and 6% triplet or greater), two or more siblings in household (27%), siblings in daycare (17%), smokers in household (36%), and smoker as the primary caregiver (16%).

Hospital courses of non-RSV and RSV-positive patients were compared, but the sample sizes were too small to conduct statistical analyses. Patients with RSV infection tended to experience longer hospital stays than those without RSV: 8.3, 9.0, and 35.5 days vs. 8.1, 2.3–41.6 days (median, range). It should be noted, however, that data are only available on three of six RSV-positive and 12 of 17 RSV-negative hospitalizations. A higher proportion of RSV-positive patients required supplemental oxygen (33.3% vs. 23.5%), and requirement for oxygen therapy was longer (7.5, 6.0–9.0 days vs. 3.0, 1.0–5.0 days). Two RSV-positive patients required intensive care unit admission and mechanical ventilation, while no RSV-negative patients required such care.

Discussion

This multinational European study was designed to confirm that palivizumab is safe and well tolerated [12]. Our study specifically targeted preterm infants 29 to 32 wGA and less than 6 months of age without chronic lung disease because little European data are currently available on the safety of palivizumab in this expanding and important subset of high-risk subjects.

The high rate of adverse events not related to palivizumab observed in this study population under-

Table 2 Summary of subjects with adverse events (AE) possibly or probably related to the study drug

Body system affected	COSTART V classification		Severity of AE, degree of seriousness, comments
	Possibly related (no.)	Probably related (no.)	
Body as a whole			
Fever	0	1	moderate, not serious
Infection[a]	1	0	severe, serious, RSV hospitalization
Digestive system			
Enteritis	1	0	mild, not serious
Respiratory system			
Bronchiolitis[a]	1	0	severe, serious, RSV hospitalization
Bronchitis[b]	1	0	mild, not serious
Increased cough	1	0	mild, not serious
Pneumonia[c]	1	0	severe, serious, bacterial
Rhinitis[b]	1	0	mild, not serious
Other			
Conjunctivitis[c]	1	0	severe, serious, bacterial

COSTART V, Coding Symbols for Thesaurus of Adverse Reaction Terms, Dictionary Version 5
[a] Events occurred in the same subject
[b] Events occurred in the same subject
[c] Events occurred in the same subject

scores the underlying fragility of these preterm infants. These were similar to those seen in the pivotal phase III palivizumab trial [12]. Palivizumab use, however, was again associated with a low incidence of drug-related adverse events. This population of European infants tolerated the drug well, and very few subjects (0.7%) discontinued palivizumab because of adverse events. These results suggest that infants born 29 to 32 wGA without chronic lung disease tolerate palivizumab well.

Preterm infants born 29 to 32 wGA who received palivizumab prophylaxis had a low incidence of RSV-related hospitalizations in this study (1.8%), a finding comparable to that observed in the pivotal trial conducted in North America and the UK [12]. This observation must be qualified by the facts that there was no control group in the present study and that hospitalizations occurred across different countries and different respiratory seasons.

We conclude that palivizumab use is safe in infants born at 29–32 wGA. The availability of palivizumab as RSV prophylaxis represents an important medical advance in the management of this high-risk preterm infant population.

Acknowledgements This study was supported by Abbot Laboratories. We gratefully acknowledge Suzann Schoenfelt for drafting the manuscript and Stacy Simpson and Paul Pollack, MD, for editorial assistance. This study complied with the current laws of the countries in which it was performed.

PROTECT Study Group Participants: E. Horak and G. Grässl, University Clinic of Pediatrics, Innsbruck, Austria; B. Resch, University Clinic of Pediatrics, Graz, Austria; D. Zaknun, University Clinic of Pediatrics, Vienna, Austria; V. Cossey, U.Z. Gasthuisberg, Leuven, Belgium; M. Kalenga, Clinique St. Vincent, Rocourt-Liège, Belgium; J. Dort, Teaching Hospital, Pilsen, Czech Republic; Z. Kokstein, Teaching Hospital, Hradec Kralove, Czech Republic; J. Kamper and S. Mortensen, Odense University Hospital, Odense, Denmark; A. Lange, Skejby University Hospital, Aarhus, Denmark; E. Salo and V. Fellman, Helsinki University Hospital, Helsinki, Finland; J. Messer and J. Beladdale, Hospital Hautepierre, Strasbourg, France; S. Marret and D. Pinquier, Hospital Charles Nicolle, Rouen, France; L. Hanssler and S. Horsch, Universitätsklinikum, Essen, Germany; W. John and C. Schindler, Klinikum Rosenheim, Rosenheim, Germany; D. Schirmer, M. Passow, and S. Schmitz, Kreiskrankenhaus Traunstein, Traunstein, Germany; J. Poeschl and S. Iben, Universitätsklinikum Heidelberg, Heidelberg, Germany; A. Andreou and V. Papavasiliou, 'Hippokrateion' General Regional Hospital of Thessaloniki, Thessaloniki, Greece; H. Dellagrammaticas and G. Kourakis, 'Aglaia Kyriakou' Regional General Children's Hospital of Athens, Athens, Greece; G. Balla, M. Berces, K. Hugyecz, and A. Mernyi, University of Debrecen, Hungary; J. Hajdu, I. Cesko, and M. Czok, Semmelweis University, Budapest, Hungary; M. Sheridan-Pereira and E. Molloy, Coombe Women's Hospital, Dublin, Ireland; A. Twomey, National Maternity Hospital, Dublin, Ireland; G. Licata and G. Maragliano, San Giovanni Ospedale, Rome, Italy; M. Grønn, Rikshospitalet, Oslo, Norway; J. Grøgaard, Ullevaal University Hospital, Oslo, Norway; J. Gadzinowski and J. Mazela, Katedra i Klinika Neonatologii, Poznan, Poland; J. Pietrzyk, M. Klimek, P. Kruczek, and K. Marchewa, Katedra Pediatrii Polsko-Amerykanskiego Instytutu Pediatrii CM UJ, Krakow, Poland; H. Guimarães, B. Guedes, G. Vasconcellos, and F. Clemente, Hospital S. João, Porto, Portugal; E. Ribeiro, A. Cunha, and A. Sousa, Hospital Fernando da Fonseca, Amadora, Portugal; A. Amin, Al-Hada Armed Forces Hospital, Taif, Saudi Arabia; J. Waly, King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia; H. Lagercrantz and S. Jonsson, Astrid Lindgren Children's Hospital, Stockholm, Sweden; I. Tessin, Queen Silvia Children's Hospital, Gothenburg, Sweden; J. Ahluwalia, Addenbrookes Hospital, Cambridge, UK; M. Drayton, University Hospital of Wales, Cardiff, Glamorgan, UK; M. McCue, W. Lam, and J.R. Groothuis, Abbott Laboratories, USA.

References

1. Hall CB (1993) Respiratory syncytial virus: what we know now. Contemp Ped November:2–11
2. Hall CB, McCarthy CA (1995) Respiratory syncytial virus. In: Mandell GL, Bennett JE, Dolin R (eds) Mandell, Douglas and Bennett's principles and practice of infectious disease, 4th edn. Churchill Livingstone, New York, pp 1501–1519
3. Meert K, Heidemann S, Abella B, Sarnaik A (1990) Does prematurity alter the course of respiratory syncytial virus infection? Crit Care Med 18:1357–1359
4. Hodson WA (1997) Normal and abnormal structural development of the lung. In: Polin RA, Fox WW (eds) Fetal and neonatal physiology, 2nd edn. Saunders, Philadelphia, pp 1033–1046
5. Mussi-Pinhata MM, Goncalves AL (1989) Serum immunoglobulin levels and incidence of infection during the first year of life in full-term and preterm infants. J Trop Pediatr 35:147–153
6. Ballow M, Cates KL, Rowe JC, Goetz C, Desbonnet C (1986) Development of the immune system in very low birth weight (less than 1500 g) premature infants: concentrations of plasma immunoglobulins and patterns of infections. Pediatr Res 20:899–904
7. Joliff CR, Cost KM, Stivrins PC, Grossman PP, Nolte CR, Franco SM, Fijan KJ, Fletcher LL, Shriner HC (1982) Reference intervals for serum IgG, IgA, IgM, C3, and C4 as determined by rate nephelometry. Clin Chem 28:126–128
8. Kim HW, Canchola JG, Brandt CD, Pyles G, Chanock RM, Jensen K, Parrott RH (1969) Respiratory syncytial virus disease in infants despite prior administration of antigenic inactivated vaccine. Am J Epidemiol 89:422–434
9. Kapikian AZ, Mitchell RH, Chanock RM, Shvedoff RA, Stewart CE (1969) An epidemiologic study of altered clinical reactivity to respiratory syncytial (RS) virus infection in children previously vaccinated with an inactivated RS virus vaccine. Am J Epidemiol 89:405–421
10. Anderson LJ, Hierholzer JC, Tsou C, Hendry RM, Fernie BF, Stone Y, McIntosh K (1985) Antigenic characterization of respiratory syncytial strains with monoclonal antibodies. J Infect Dis 151:626–633
11. Crowe JE, Englund JA (2000) Future prevention strategies. In: Weisman LE, Groothuis JR (eds) Contemporary diagnosis and management of respiratory syncytial virus. Handbooks in Health Care, PA, pp 176–200
12. The IMpact-RSV Study Group (1998) Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. Pediatrics 102:531–537
13. Declaration of Helsinki—Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects. Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964. Amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975, 35th World Medical Assembly, Venice, Italy, October 1983, 41st World Medical Assembly, Hong Kong, September 1989, and the 48th General Assembly, Somerset West, Republic of South Africa, 1996