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REVIEW ARTICLE

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Development and use of palivizumab (Synagis): a passive immunoprophylactic agent for RSV

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Abstract Palivizumab (Synagis; Abbott Laboratories), a humanized, monoclonal antibody, prevents lower respiratory tract infection by respiratory syncytial virus (RSV). RSV causes significant morbidity and mortality in young children worldwide and is particularly severe in pre-term infants, children with cardiopulmonary disease, and the immunosuppressed population. The first such genetically engineered agent to be used effectively against a human infectious disease, palivizumab significantly reduces the number of hospitalizations caused by RSV in high-risk infants. This article reviews the preclinical development and clinical experience of palivizumab.

Key words Respiratory syncytial virus (RSV) · Bronchiolitis · Chronic lung disease (CLD) · Bronchopulmonary dysplasia (BPD) · Prematurity · Humanized monoclonal antibody · Palivizumab (Synagis) · IMpact-RSV study

Introduction

Since its initial discovery in chimpanzees and subsequent isolation from children diagnosed with pneumonia and bronchiolitis in the late 1950s, respiratory syncytial virus (RSV) has been implicated as the primary viral etiologic agent in serious lower respiratory tract infections (LRTIs) in infants and young children worldwide.[1] RSV results in significant morbidity and mortality in both developed and developing countries, and is responsible for approximately 4 million deaths annually. Preterm infants are particularly vulnerable to the severe sequelae of RSV infection because of their immature immune and pulmonary systems. Driven by the physical, social, and economic costs of RSV, efforts have been ongoing for over four decades to prevent and treat infections caused by RSV. This article focuses on research advances that have led to the development and use of the humanized monoclonal antibody palivizumab as a means of passive immunoprophylaxis in high-risk preterm infants and children.

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Rationale for RSV prophylaxis

Respiratory syncytial virus (RSV) is a ubiquitous pathogen. Serologic evidence of infection can be found in nearly all children by age 2 years.[2] RSV in vulnerable populations – premature infants, otherwise healthy infants under age 6 months, and children with chronic lung or heart disease or immunodeficiency – can lead to hospitalization for the administration of supplemental oxygen, intravenous fluids, and/or bronchodilator, antiviral, or corticosteroid medications and mechanical ventilation. Unfortunately, no specific therapy has been proven to be of definitive value in the treatment of this frequently serious illness, and supportive care is all that can be currently offered. Prevention of RSV infection is therefore of primary importance. Hospital infection control practices to avert nosocomial outbreaks are essential, as is parental education regarding disease transmission, recognition of symptoms, and avoidance of factors that increase the risk for infection – day-care attendance, exposure to secondhand smoke, and crowding in the home. Continuing efforts to develop a vaccine against RSV that is both safe and effective have been thwarted by a variety of issues unique to the young infant and to RSV.

Obstacles to vaccine development

Protection against RSV is vital for premature infants in particular, because these infants lack the maternally ac-

quired passive immunity usually conferred during the last trimester of pregnancy. Infants under 6 months of age would benefit most from vaccination because they tend to develop the most severe illness. Unfortunately, these infants lack an adequately developed immune system to generate an effective immune response upon exposure to antigen introduced via vaccination. Conversely, maternal antibodies to RSV present in full-term infants might neutralize a live, attenuated vaccine before they were able to mount an immune response. A formalin-inactivated vaccine, developed in the 1960s, paradoxically exacerbated pulmonary illness in vaccinated children who were subsequently exposed to wild-type virus in the following RSV season.[3] Serious safety concerns related to this experience persist as vaccine development efforts continue. Furthermore, the existence of two subtypes and multiple strains of RSV, along with the common occurrence of reinfection, would probably require multiple boosters of a vaccine that would have to include multiple subtypes and strains – a technically challenging feat that has yet to be accomplished. Finally, active immunization might interfere with other pediatric vaccinations given in the same time frame.

Success with passive immunoprophylaxis has been greater, although polyclonal immunoglobulin products that preceded the development of palivizumab were either ineffective or had other drawbacks. To adequately protect against RSV infection, an agent has to be effective against both RSV subtypes, A and B, and has to have a reasonable duration of action. In addition, it should be safe and relatively easy to administer. The RSV – hyperimmune globulin (RSV-IGIV, RespiGam, MedImmune, Gaithersburg, MD, USA), required intravenous administration in large volumes. This presented serious obstacles for premature infants with poor intravenous access. In addition, excessive fluid volumes precipitated cardiac complications in some infants.[4] Furthermore, polyclonal, hyperimmune globulins are derived from human blood, thus posing a theoretical risk in terms of infectious disease transmission.

Background on RSV

Respiratory syncytial virus (RSV) is an RNA virus with a single strand of genetic material encoding for ten proteins. The two most important such proteins, in terms of pathogenicity and immunogenicity, are the F and G glycoproteins located on the viral surface. The G glycoprotein mediates viral attachment to respiratory epithelial cells, while the F (fusion) glycoprotein allows fusion of the viral envelope with the respiratory cell's lipid membrane. It is also responsible for the fusion of adjoining cells to form syncytia, for which the virus is named. While RSV has two subtypes and numerous strains, the F protein is well conserved across all variants, and thus is an ideal target for monoclonal antibody development. Antibody targeted to the highly conserved A epitope of the F protein prevents infection by impeding virus-to-host cell membrane fusion, subsequent cell-to-cell transmission, and viral replication.

RSV epidemiology and clinical features in Japan

Takeuchi[5] was the first to perform a prospective study to characterize the epidemiologic and clinical features of RSV in Japanese children. In a prospective study of four RSV epidemics, from 1979–1983, he demonstrated that RSV in Japan peaked in December–January, in a finding similar to that of epidemics in other temperate northern hemisphere countries,[5] He also described the clinical characteristics of 124 children hospitalized with RSV disease in Kawasaki Municipal Hospital during the 1982–1983 RSV season. He observed that 78% of the hospitalized patients had evidence of lower respiratory infection and 50% of all hospitalized patients were less than 11 months of age. Takeuchi observed that the clinical features of RSV disease in infants less than 3 months of age often differed from those in older infants. Older infants usually presented with dyspnea, acidosis, and low O2 and high CO2 levels. Three cases of near-miss sudden infant death syndrome (SIDS) were observed in the very young (<3 months) infants; these infants were afebrile throughout their clinical course. Saijo et al.[6] examined a group of 317 Japanese children 13 years of age and younger who were hospitalized for LRTIs between April 1991 and March 1992. The average age of these children was 11 months. Investigators found that 70.5% of the youngest children (<2 years old) and 64.7% of all children tested positive for RSV. RSV accounted for 42.4% of bronchopneumonias, 64.1% of bronchiolitis (all ages), and 74.1% of bronchiolitis in infants under 1 year of age. Similar trends continued in the next RSV season.[7] Overall, 162 children required hospitalization for bronchiolitis before age 3 years. Seventy-six percent were RSV-antigen positive; 43.5% were ≤6 months old. No differences in incidence of RSV were noted between the sexes.

Long-term sequelae of RSV disease

RSV infection has been associated with long-term pulmonary consequences. The association of early RSV illness with childhood reactive airways disease (RAD/asthma) has been documented in several clinical trials. One such trial, conducted by Sigurs and colleagues,[8] followed 47 infants hospitalized for RSV bronchiolitis and 93 matched controls to the age of 7 in a prospective study. They reported a tenfold increased prevalence of asthma (30% versus 3%; $P < 0.001$) in the infants previously hospitalized with RSV. Such data, suggest that RSV infection at a young age may predispose children to RAD.[8]

Development of palivizumab

A series of murine monoclonal antibodies was raised against RSV, from which the one with the strongest binding affinity to the F protein was selected. The genes encoding

the complementarity-determining regions (CDRs) were isolated from cells producing that antibody and were incorporated into human genes that encode for the light and heavy chains of a human IgG antibody.[9] IgG was chosen for its long half-life (28 days), which would allow for a convenient monthly dosing schedule throughout the RSV season. The mouse CDRs account for only 5% of the antibody molecule – the remaining 95% is of human origin.

The recombinant genes containing the mouse CDRs and the human immunoglobulin chains were then inserted into a plasmid from *Escherichia coli*. This plasmid was combined with mammalian hybridoma cells, which are immortal in culture and have the ability to produce antibody. A master cell bank was created, from which samples are taken to initiate cultures used in the production of palivizumab. Quality control measures are incorporated throughout the manufacturing process to safeguard against contamination and ensure consistent quality and potency of the product.[9]

Preclinical studies in the cotton rat

Johnson et al.[10] conducted studies in the cotton rat to determine the biologic properties of this humanized monoclonal antibody. The rats were injected with antibody and the following day were infected intranasally with either RSV subtype A or subtype B.[10] The antibody was effective against both subtypes, resulting in a reduction in viral replication of greater than 99% at an intravenous dose of 2.5 mg/kg. This dose resulted in serum antibody concentrations of around 25–30 μg/ml.[10] This serum concentration was set as the target value to achieve in humans to ensure that the lower respiratory tract was protected against infection with RSV.

Additional studies were conducted to evaluate whether RSV would become more virulent upon primary or secondary challenge in the presence of passively acquired anti-RSV antibody. The concern was whether this antibody, in noninhibitory concentrations, could cause enhanced viral replication or virally mediated pulmonary pathology during primary exposure (reminiscent of the formalin-inactivated virus experience), or permit the development of antibody-resistant strains. There was no increase in viral load or virus-related pulmonary pathology noted upon two challenges. In studies designed to detect antibody-resistant mutants, lung tissue from only one animal that had received a very low dose of antibody (0.0032 mg/kg) grew a single viral plaque. Johnson and colleagues[10] further noted that animals that had been passively immunized were completely resistant to infection after clearance of antibody, suggesting that palivizumab administration does not inhibit a protective immune response to RSV.

In summary, experiments in the cotton rat showed that palivizumab had potent neutralizing and fusion-inhibiting properties for both RSV subtypes A and B, which were dose-dependent. At the same time, it did not enhance viral replication or lung pathology upon subsequent exposure to RSV. The promising results of these studies in the cotton rat were extremely useful in understanding the behavior of RSV virus in the presence of a humanized monoclonal antibody, and paved the way for human studies.

Clinical trials with palivizumab

The safety and efficacy of palivizumab was investigated in the IMpact-RSV Study.[11] This large ($n = 1502$), multicenter, randomized, double-blind, placebo-controlled, phase III study of children from 139 centers in the United States, United Kingdom, and Canada was conducted during the 1996–1997 RSV season. The primary objective of the study was to determine whether palivizumab would decrease hospitalization rates for premature infants (≤35 weeks' gestation and ≤6 months of age) and for children up to 2 years old with active bronchopulmonary dysplasia (BPD) requiring treatment within the past 6 months. Subjects received either 15 mg/kg palivizumab or placebo intramuscularly (IM) once a month for 5 months during the RSV season. Excluded from the study were those children who were expected to require prolonged hospitalization (>30 days), those who required mechanical ventilation, had a history of current or previous RSV infection, or hepatic, congenital heart, or renal disease, seizure disorder, history of immunodeficiency or an allergy to IgG, had received RSV-related vaccine products (such as RSV-IVIG), and/or who had a life expectancy of less than 6 months. Secondary study endpoints are listed in Table 1.

In the IMpact-RSV study, 500 children were randomized to the placebo group and 1002 to receive palivizumab. The two groups were well-matched for sex, race, weight, age, and number of people in the household, birth weight, number of weeks' gestation, incidence of multiple births, whether there were other children in the home, presence in day care, and family history of atopy.

A total of 1486 children (99% of participants) completed the study. There was an overall 55% ($P < 0.001$) reduction in hospitalization for the palivizumab group; the placebo group had a hospitalization rate of 10.6% and the palivizumab group's hospitalization rate was 4.8%. Significant reductions were also observed in subsets of the investigational population. Preterm infants without BPD born between 32 and 35 weeks' gestation had an 82% reduction in hospitalization, from 10.0% to 1.8%. A 39% reduction in

Table 1. Primary and secondary endpoints of the IMpact-RSV study[11]

Primary
- Hospitalization with confirmed case of RSV

Secondary
- Incidence of hospitalizations
- Total number of days in hospital
- Total number of days requiring supplemental oxygen
- Total number of days with moderate to severe lower respiratory tract illness (LRI score = 3)
- Total number of days spent in the intensive care unit
- Total number of days necessitating mechanical ventilation
- Incidence of otitis media

RSV, Respiratory syncytial virus; LRI, lower respiratory tract infection

hospitalization rates, from 12.8% to 7.9%, was noted for infants with BPD. With the exception of otitis media, all secondary endpoints were achieved. Statistically significant reductions were observed in intensive care unit (ICU) admissions, total hospitalizations, and those related to respiratory illness, numbers of days in the hospital, days of required oxygen administration, and days with moderate to severe LRTI. Adverse events were rare, and were comparable in both the palivizumab and placebo groups, and none were judged to be medication-related. This phase III investigation concluded that palivizumab was effective, safe, and well tolerated.

Pharmacokinetic and safety bridging studies

Bridging studies were conducted to determine whether the safety and efficacy of palivizumab established in the IMpact-RSV study would be observed in the Japanese population. In a phase I safety trial, palivizumab was given to six Japanese and six overseas healthy adult volunteers to evaluate dose, safety, and pharmacokinetics. The dosages evaluated were 3 mg/kg IM, 3 mg/kg intravenous (IV), 10 mg/kg IV, and 15 mg/kg IV. The larger doses were administered IV because of the large volumes required. No significant differences were found between the Japanese and overseas groups in terms of maximum concentrations, area under the curve (AUC), half-life, clearance, and trough concentrations.[12] No adverse reactions were observed. Phase II bridging studies were subsequently conducted in Japanese children. Thirty-one children (19 preterm, 13 with BPD (also known as chronic lung disease), were given 15 mg/kg of palivizumab IM. There were no significant differences in mean serum trough palivizumab levels, serum concentrations, and AUC between the Japanese and overseas children, nor were any adverse reactions reported. One child developed a mild RSV upper respiratory tract infection (URI), which did not require hospitalization.[12]

Over 700 RSV isolates from both subtypes A and B from 19 countries have been tested for palivizumab binding. These included 23 isolates (13 A strains and 10 B strains) from Japan. All isolates from all countries were successfully bound by palivizumab.[11]

Post-licensing clinical experience

Based on the results of the IMpact-RSV study, palivizumab was approved for use in 1998 in the United States and in 1999 in Europe. Palivizumab received regulatory approval in Japan in February 2002.

Since 1998, phase IV trials have examined RSV hospitalization rates for preterm children with and without BPD in the presence or absence of prophylaxis with palivizumab. Simoes and Groothuis[13] performed a metaanalysis of 18 of these studies, which were conducted in the United States, United Kingdom, Canada, France, the Netherlands, and other European Union countries. Prospective and retrospective and comparative and noncomparative studies were included. Children were divided into three subgroups: children less than age 2 years with chronic lung disease (CLD), children born at 29–32 weeks' gestational age without CLD, and children born at 32–35 weeks' gestational age without CLD. Hospitalization rates were computed by dividing the total number of subjects with one or more RSV-related hospitalizations by the total number of subjects in the study.

The study found that nonprophylaxed and palivizumab-prophylaxed RSV hospitalization rates were 17.9% and 5.6%, respectively, in the CLD children, 10.2% and 2.0%, respectively, for children born at 29–32 weeks' gestational age, and 9.8% and 1.5%, respectively, for children born at 32–35 weeks' gestational age. These findings provide strong support for the use of palivizumab in high-risk infants and children (Table 2).

Surveillance data regarding tolerance and adverse events

Postmarketing pharmacovigilance has not identified any serious adverse events among recipients of palivizumab beyond those identified in the IMpact-RSV study. Approximately 272 879 patient exposures to palivizumab occurred between October 1998 and June 2001. None of the 121 deaths in these patients were attributed to palivizumab. The incidence of mild or moderate adverse events, including upper respiratory tract infection, otitis media, rhinitis, fever, rash, cough, diarrhea, wheeze, nervousness, or bronchiolitis ranged from 0.3% to 5.8%, as reported by physicians administering the injection and through telephone contact with parents of recipients, respectively. Serious adverse events, such as dyspnea, asthma, pneumonia, and fever, occurred in only 0.1% of the group reported on by physicians and in 2.8% of the group contacted by telephone.[13] No serious injection-site reactions, such as muscular atrophy or contracture, have been reported.

Summary

Respiratory syncytial virus (RSV) is one of the most important causes of lower respiratory tract illness in infants and children worldwide and causes significant morbidity, particularly for preterm infants and those with cardiac, pulmonary, and immunodeficiency states. Prevention is vital for those at greatest risk. Palivizumab is currently the only proven and licensed prophylaxis against lower respiratory tract infection caused by RSV. Randomized clinical trials and outcomes surveys support its effectiveness and safety in reducing RSV-related hospitalization rates in high-risk infants. Palivizumab may be given in an outpatient setting via the intramuscular route once per month during the RSV season. Its convenient route of administration and good tolerability profile enhance compliance with this monthly

Table 2. Combined analysis of prophylaxed and nonprophylaxed children in three subgroups: (1) BPD/CLD, less than 2 years of age; (2) 29–32 weeks' gestational age (wGA) without CLD; and (3) 32–35 wGA without CLD

Infants with BPD/CLD <2 years of age (n = 3675)

Study (country)	RSV hospitalization rates			
	Unprophylaxed patients		Palivizumab patients	
	Rate	(n)	Rate	(n)
Groothuis (USA)[14]	36.7%	(30)		
PREVENT (USA)[15]	17.4%	(149)		
Stevens et al. (USA)[16]	25.2%	(131)		
Greenough et al. (UK)[17]	19.1%	(235)		
IMpact-RSV (USA/Can/UK)[11]	12.8%	(266)	7.9%	(496)
Outcomes 1998–1999 (USA)[18]			4.0%	(402)
Outcomes 1999–2000 (USA)[19]			3.9%	(795)
COMPOSS (Canada)[20]			6.0%	(95)
PharmaScope (NL)[21]			3.4%	(88)
ATU (France)[22]			7.6%	(506)
Registry 2000–2001[23]			5.8%	(482)
Weighted mean rate	**18.4%**	**(811)**	**5.6%**	**(2864)**

Infants 29–32 wGA without CLD (n = 4854)

Study (country)	RSV hospitalization rates			
	Unprophylaxed patients		Palivizumab patients	
	Rate	(n)	Rate	(n)
IRIS 1 (Spain)[24]	10.1%	(456)		
IRIS 2 (Spain)[25]	12.9%	(827)		
Stevens et al. (USA)[16]	7.6%	(662)		
IMpact-RSV (US/Can/UK)[11]	8.5%	(142)	1.6%	(313)
Outcomes 1998–1999 (USA)[18]			2.0%	(506)
Outcomes 1999–2000 (USA)[19]			2.3%	(690)
COMPOSS (Canada)[20]			1.3%	(199)
PharmaScope (NL)[21]			0.8%	(124)
Registry 2000–2001 (USA)[23]			2.3%	(650)
International Study W00-355[26]			2.1%	(285)
Weighted mean rate	**10.3%**	**(2087)**	**2.0%**	**(2767)**

Infants 32–35 wGA without CLD (n = 2829)

Study (country)	RSV hospitalization rates			
	Unprophylaxed patients		Palivizumab patients	
	Rate	(n)	Rate	(n)
IMpact-RSV (USA/Can/UK)[11]	9.8%	(123)	2.0%	(250)
Outcomes 1998–1999 (USA)[18]			1.5%	(548)
Outcomes 1999–2000 (USA)[19]			1.3%	(972)
Registry 2000–2001 (USA)[23]			1.6%	(936)
Weighted Mean Rate	**9.8%**	**(123)**	**1.5%**	**(2706)**

BPD, Bronchopulmonary dysplasia; CLD, chronic lung disease; RSV, respiratory syncytial virus
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regimen. Recent bridging studies have demonstrated that palivizumab has identical pharmacokinetics and safety profiles in high-risk Japanese and Caucasian children, and guidelines for its use have been developed.

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