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Review Article

Prevention of respiratory syncytial virus infections in high-risk infants by monoclonal antibody (palivizumab)

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Abstract Respiratory syncytial virus (RSV) is a major viral pathogen which causes serious respiratory illness in infants and children worldwide. Palivizumab (Synagis) is an anti-RSV monoclonal antibody administered intramuscularly for the prevention of severe RSV respiratory disease in high-risk infants and young children. The IMpact-RSV trial, the pivotal multicenter, randomized, placebo-controlled trial performed in the USA, Canada and the United Kingdom demonstrated an overall 55% reduction in hospitalization rate due to RSV infection in preterm infants (≤ 35 weeks gestation) with and without chronic lung disease (CLD). Subgroup analysis in premature infants without CLD revealed an even greater reduction in RSV hospitalization rates (78%). Adverse events were infrequent and did not differ between placebo and palivizumab groups. Injection site reactions were infrequent and mild; no differences were observed between palivizumab and placebo subjects. Palivizumab does not interfere with administration of other pediatric vaccines. Comprehensive parent education programs regarding prevention of infection, avoidance of risk factors for infection, careful adherence to infection control policies, and recognition of early symptoms of RSV infection remain important components of RSV prevention strategies. In light of the lack of effective vaccines for this serious health risk, palivizumab offers the only option for prophylaxis against RSV disease in high-risk infants.

Key words high-risk infant, palivizumab, prematurity, respiratory syncytial virus, Synagis.

Respiratory illness is reported to be the most frequent cause of rehospitalization of preterm infants, and respiratory syncytial virus (RSV) is the most common cause of viral respiratory infection, illness and hospitalization in this group.[1,2] Years of research have failed to yield a safe and effective RSV vaccine. However, using genetic engineering technology, a humanized monoclonal antibody, palivizumab, has been developed that binds to the RSV fusion (F) protein and neutralizes the virus. Palivizumab (to be marketed under the trade name Synagis) is the first monoclonal antibody proven to be efficacious for the immunoprophylaxis of an infectious disease in humans. The results of the IMpact-RSV trial, a large phase III, randomized, placebo-controlled trial conducted in the USA, Canada, and the United Kingdom, demonstrated an overall 55% reduction in hospitalization due to RSV infection in high-risk infants prophylaxed with palivizumab.[3] The indications for palivizumab use are largely based on this trial. Bridging safety and pharmacokinetic studies on palivizumab were also conducted and the results validate the IMpact-RSV trial findings in Japanese patients. A group of Japanese pediatricians, neonatologists, and infectious disease specialists with particular expertise in the management of RSV infections and high-risk infants have collaborated to define usage guidelines for palivizumab. In the course of the collaboration, these physicians: (i) reviewed the scientific evidence serving as the basis for the clinical use of humanized monoclonal antibody in the immunoprophylaxis of RSV infections; (ii) shared local and overseas experience and practice patterns in the treatment of RSV infection; and (iii) formulated recommendations for the use of palivizumab. This paper summarizes the background information available on RSV and palivizumab, and presents the consensus of the collaborating physicians regarding recommendations for use of palivizumab in high-risk infants and children in Japan. Similar recommendations have been issued in the USA by the American Academy of Pediatrics and by other consensus groups worldwide.[4–6]

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Background

RSV

Morris *et al.* isolated a virus causing coryza from chimpanzees in 1956 and named it chimpanzee coryza agent (CCA).[7] Chanock *et al.* isolated comparable viruses from children with pneumonia and laryngotracheobronchitis which formed syncytia in tissue culture and were virtually indistinguishable from CCA.[8] The virus was renamed respiratory syncytial virus (RSV), and it has proven to be a major cause of severe respiratory illness in infants and children worldwide.

Respiratory syncytial virus is a single-stranded RNA virus encoding for 10 proteins. In terms of infectivity and immunogenicity, the most important proteins are the two surface glycoproteins, G and F. The G protein mediates viral attachment to host respiratory epithelial cells, while the F protein mediates viral penetration into the respiratory epitheilial cell and subsequent spread to adjacent cells through fusion of cell membranes and formation of syncytia.[9] Respiratory syncytial virus has two subtypes, A and B, and numerous strains. The F protein is highly conserved within all RSV strains, both temporally and geographically, while the G protein exhibits broad heterogeneity.[10]

The burden of RSV disease

Respiratory syncytial virus is the most common cause of bronchiolitis and pneumonia in infants and children.[11] It is estimated that RSV accounts directly or indirectly for 600 000–1 000 000 deaths annually in children under 5 years of age worldwide.[12]

In Japan, RSV epidemics occur annually, beginning from October to December, peaking between November and February, and declining from March to May. More than 40% of outpatients are infected with RSV during the peak of the epidemic (Y Takeuchi, pers. comm., 2000). Greater than 25% of RSV hospitalization cases may occur in the summer months.[13] In a study conducted in northern Japan, Saijo *et al.* investigated the incidence of RSV in children up to 13 years of age hospitalized for lower respiratory tract infection (LRTI) from April 1991 to March 1992.[13] In the 317 patients evaluated, 70.5% of children less than 2 years of age were RSV positive. The RSV positive cases accounted for 42.4% of bronchopneumonias, 64.1% of bronchiolitis in all ages, and 74.1% of bronchiolitis in infants less than 12-months-old. At the peak of the season, 64.7% of all cases were RSV-antigen positive.

Saijo *et al.* continued their study for a second year.[14] During the 2-year study period, 162 children under 3 years of age were hospitalized with acute bronchiolitis; 76.5% were RSV-antigen positive, and 43.5% of patients with acute RSV bronchiolitis were 6-months-old or less. The average age of RSV bronchiolitis patients was 11.2 months. The male:female ratio was 1.1:1.0.[14]

Prematurity, defined in Japan as less than or equal to 37 weeks' gestation, has been identified as the major risk factor for severe RSV disease. The premature birth rate in 1999 in Japan was 5.4% of the total birth rate.[15] This relatively low rate may be attributed to several factors, including more consistent prenatal care, a more homogeneous population, and less (but increasing) use of *in vitro* fertilization (IVF) procedures. As the use of IVF procedures increases, the prematurity rate in Japan may rise. There is a greater than 80% survival rate for infants born less than 1000 g (extremely low-birthweight, ELBW (WHO criteria)) in Japan's major neonatal intensive care institutions. Consequently, there is significant morbidity for these infants, including respiratory illness (mainly chronic lung disease (CLD)). In a national survey of ELBW infants born in 1990, at 3 years of age, 3.8% of the children were on home oxygen therapy and 10.9% had recurrent respiratory infection.[16]

Several factors contribute to severe RSV disease in preterm infants. Maternal IgG antibodies cross the placenta in the final weeks of gestation and provide protection for a full-term newborn against RSV disease. However, in the infant born prematurely, these antibodies do not achieve protective levels.[17,18] Anatomically small airways predispose these infants to bronchial obstruction. Premature infants also have poorly developed cellular immunity, which is important for viral clearance from the lungs. Chronic lung disease (formerly designated bronchopulmonary dysplasia), a frequent complication of prematurity, combined with barotrauma and high oxygen concentrations, results in limited pulmonary reserve and an increased susceptibility to serious RSV illness.[19] Additional children at risk to develop severe RSV disease include those with other forms of CLD,[20] congenital heart disease,[21] and immunodeficiency,[22] such as congenital severe combined immunodeficiency, AIDS, HIV infection or resulting from chemotherapy or organ transplantation. Selection of infants who will derive the greatest benefit from immunoprophylaxis necessitates the identification of those infants with underlying physical and demographic factors that place them at greatest risk of hospitalization and/or mechanical ventilation if infected with RSV.

Several recently published studies suggest that there is an association between RSV bronchiolitis in infancy and the development of reactive airway disease later in life. The Tucson Children's Respiratory Study reported increased risk for frequent wheezing (odds ratio (OR) 3.2) and infrequent wheezing (OR 4.3) following mild RSV lower respiratory tract infection (not requiring hospitalization) up to age 11. The risk decreased with age and was not statistically significant by age 13.[23]

Sigurs *et al*. prospectively followed 47 infants hospitalized for RSV bronchiolitis and 93 matched controls for incidence of subsequent asthma.[24] At the age of 7 years, the cumulative prevalence of asthma was 30% in the RSV group versus 3% in the control group ($P < 0.001$). The incidence of recurrent asthma was 23% in the RSV group and 2% in the control group ($P < 0.001$).

Prevention

Options for treatment of severe RSV lower respiratory tract infection are limited and often controversial.[25] Ribavirin, an antiviral agent approved overseas for RSV, has questionable efficacy and many concerns are associated with its use. Bronchodilators, an obvious choice in obstructive airway disease, have not uniformly proven to be beneficial. Corticosteroids are a theoretical option to treat the inflammatory aspects of RSV disease, but clinical trials have not demonstrated efficacy and the potential toxicity of this treatment approach makes it unacceptable. Therefore, therapy for RSV lower respiratory tract disease is mainly supportive care, including supplemental oxygen, fluids, careful monitoring and ventilation in the most severe cases. Prevention, rather than treatment of severe RSV disease, is the preferred approach, particularly in high-risk infants and young children.

Vaccines

Prevention of RSV disease in small infants has been problematic and the development of a vaccine to RSV has thus far been unsuccessful. Obstacles to RSV vaccine development include the following:

1 The risk of infection is highest for the very young infant (< 6 months of age). Immunization would therefore be necessary almost immediately after birth, at which time the immune system is still immature. Both the RSV F and G proteins (the epitopes that elicit neutralizing antibody formation) are glycoproteins that are weakly immunogenic in early infancy.
2 Circulating maternal antibody, if present, would neutralize live attenuated RSV vaccine before the infant had the opportunity to mount an immune response.
3 Natural immunity against RSV is short-lived and often does not protect against recurrence of infection, even in individuals with healthy, mature immune systems. Therefore, repeated boosters would most likely be necessary.
4 The existence of two subtypes and multiple strains of RSV makes it difficult to prepare a vaccine that would afford broad protection. A likely vaccine candidate would need to contain both F and G proteins.
5 Experience with a formalin-inactivated vaccine in the 1960s resulted in enhanced RSV pulmonary disease severity in very young vaccinees and raised serious safety concerns.[26] These concerns have not yet been resolved.

Passive prophylaxis

Administration of both standard and hyperimmune polyclonal immune globulin has been investigated for the prevention of RSV disease. In clinical trials conducted in the late 1980s, standard immune globulin was administered monthly to high-risk infants during the RSV season. There were no major side-effects and a trend towards a reduction in hospital days was observed. However, no statistically significant decrease in the severity of RSV disease was seen. This observation was attributed to insufficient anti-RSV antibody concentrations present in standard immune globulin.[27,28] Subsequently, a hyperimmune RSV polyclonal globulin (RSV-immunoglobulin intravenous (IGIV), RespiGam) was developed. Five infusions of RSV-IGIV given at monthly intervals were administered during the RSV season to preterm infants in two multicenter, randomized controlled trials. The results demonstrated a 41 to 63% reduction in RSV-related hospital admissions.[29,30] Despite a favorable safety and efficacy profile, a number of drawbacks were associated with RSV-IGIV usage. These included:

1 Difficulty of administration (i.v.)
2 Large fluid load (15 mL/kg)
3 High protein load (750 mg/kg)
4 Theoretical risk of transmitting blood-borne pathogens
5 Supply shortages
6 Need to postpone live vaccines (e.g. measles/mumps/rubella, varicella).

A trend towards increased mortality rates was observed in children with cyanotic congenital heart disease (CHD) who had received RSV-IGIV.[29,31] Consequently, administration of RSV-IGIV to infants with complex CHD is contraindicated. Currently, availability of RSV-IGIV is extremely limited and its use has been superseded by palivizumab.

The observation that anti-RSV neutralizing antibodies were effective in preventing serious RSV disease provided the proof of principle that led to the development of RSV-specific monoclonal antibodies. The nasal mucosa is the portal of entry for RSV. Hence, it was thought that protection might be obtained by applying anti-RSV IgA antibody topically. A murine anti-RSV IgA antibody was developed, however, a large phase III studies failed to demonstrate efficacy.[32]

Two separate IgG_1 monoclonal antibodies have been developed. The first, SB 209763, is an IgG_1 directed against the C epitope of the RSV F protein. A large, multicenter, placebo-controlled clinical trial, in which more than 800 children in the USA and Europe received 10 mg/kg monthly, failed to demonstrate a statistically or clinically significant reduction in RSV-related hospitalizations. This failure was

attributed to two factors: lack of potency and insufficient dose.[33,34]

The second IgG_1 monoclonal antibody, palivizumab, is also directed against the RSV F protein, but to a different epitope (A). In a large, double-blind, randomized, placebo-controlled trial (IMpact-RSV), five monthly intramuscular (i.m.) injections of 15 mg/kg palivizumab or placebo were administered to 1502 premature infants with or without CLD during the RSV season.[3] Hospitalizations due to RSV disease (the primary end-point) were reduced by 55% in the palivizumab group ($P < 0.001$). There were no significant differences between palivizumab and placebo groups in the frequency and/or type of adverse events.

Palivizumab

Mechanisms of action

Two RSV surface glycoproteins elicit a neutralizing antibody response, G and F proteins. The G protein, responsible for viral attachment to the respiratory endothelial cell, is a poor candidate for development of a monoclonal antibody because of its heterogeneity between the major RSV subtypes, A and B. Conversely, the F protein, responsible for viral fusion with the cell and formation of syncytia, is well conserved between RSV strains, over time and geography.[10] Palivizumab is a humanized monoclonal antibody directed against the RSV F protein A epitope. Its neutralizing activity prevents RSV from fusing with the respiratory endothelial cell membrane, thereby preventing replication.[35] Palivizumab is a recombinant monoclonal antibody, hence it is not derived from pooled human immune globulin. It is free of potential contamination by infectious agents and can be produced in large batch lots, ensuring adequate supply.

Pharmacokinetics

Dosing studies performed first in the cotton rat suggested that trough palivizumab serum concentrations of 25–30 μg/mL resulted in a mean of >99% reduction of RSV titers in the lungs.[36,37] In previous studies with RSV-IGIV, this 99% reduction correlated well with human protection.[29,30] Based on this paradigm, the dosage of 15 mg/kg was selected. Because the average serum half-life of palivizumab was found to range between 18 and 21 days, palivizumab is dosed every 28–30 days to maintain adequate trough serum concentrations throughout the RSV season.[35]

A pharmacokinetic study was performed in Japanese adults to obtain safety data on palivizumab prior to proceeding with phase I/II studies in pediatric patients.[38] Six Japanese and six overseas healthy adult volunteers were administered palivizumab 3 mg/kg i.m., 3 mg/kg i.v., 10 mg/kg i.v. and 15 mg/kg i.v. In this study, palivizumab was administered intravenously rather than intramuscularly in some cases due to the large volume of the dose required for an adult. Previous studies had established similar pharmacokinetic profiles for both routes of administration.[37] There were no significant differences in maximum concentration achieved, area under the curve (AUC), half-life, clearance and trough concentrations between the Japanese and overseas adult groups. A phase II study was conducted in which 31 infants, 19 with prematurity and 13 with CLD, were given 15 mg/kg per dose of palivizumab intramuscularly. Mean trough levels, serum concentrations and AUC were comparable between the Japanese and overseas infants.[38] Adverse reactions were low and comparable to overseas infants. No significant local reactions were observed.

Binding to RSV isolates

There is a theoretical possibility that RSV strains exist that have genetic variation in the A epitope of the F protein. If this were the case, palivizumab would not bind to such strains, and therefore, would fail to provide protection against infection with these strains. More than 700 RSV isolates have been collected from 19 countries and tested for their ability to bind palivizumab. A subset of these has also been tested for the ability of palivizumab to neutralize the virus. Palivizumab bound to and neutralized all isolates tested.[39] An additional 23 isolates were collected in Japan, 13 of subtype A and 10 of subtype B. These isolates were tested for their ability to bind palivizumab; all bound the antibody (T Tsutsumi, pers. comm., 2000).

Article reviews and results

Clinical efficacy of palivizumab

The efficacy of palivizumab was established in a large, multicenter, double-blind, randomized clinical trial (IMpact-RSV).[3] A total of 139 centers in the USA, Canada and the United Kingdom participated. The trial was conducted during the RSV season in 1996–1997. Infants and children were eligible to enrol if they were: (i) 35 weeks' gestation or less and 6 months of age or younger at the start of the RSV season or (ii) 24-months-old or younger and had a clinical diagnosis of CLD requiring medical treatment (i.e. supplemental oxygen, steroids, bronchodilators, or diuretics) within 6 months of RSV season onset.

A total of 1502 children were randomized in a 2:1 ratio between the palivizumab (1002) and placebo (500) groups. This large sample size allowed for subgroup analysis at trial conclusion. Risk factors and demographics were well balanced between treatment groups. Children received i.m. injections of either 15 mg/kg palivizumab or placebo every

30 days, commencing at the start of the RSV season, for a total of five doses.

Administration of palivizumab resulted in a 55% overall reduction in RSV-related hospitalization, which was the primary end-point (10.6 to 4.8% in placebo *vs* palivizumab, $P < 0.001$). Most secondary end-points were also achieved. Hospital days per 100 children were decreased from 62.6 in the placebo group to 36.4 in the palivizumab group ($P < 0.001$). Oxygen requirement per 100 children was reduced from 50.6 days in the placebo group to 30.3 days in the palivizumab group ($P < 0.001$). The number of days with a LRTI score of 3 days or greater was also reduced (47.4 days *vs* 29.6 days, $P < 0.001$). The incidence of intensive care unit admission was lower in the palivizumab group ($P = 0.026$). There were no differences in hospital course or mechanical ventilation days once RSV disease was established. Incidence of otitis media was similar between treatment groups. There were no differences between groups in incidence or total days of respiratory hospitalization due to non-RSV respiratory viruses. No significant differences were observed in either the types or rates of adverse events or in antipalivizumab antibody formation between palivizumab and placebo groups.

Subgroup analysis

Palivizumab reduced the hospitalization rates of clinical RSV illness in all subgroups evaluated.[3] Preterm infants without CLD had a 78% reduction in hospitalization (8.1% placebo *vs* 1.8% palivizumab, $P < 0.001$). Preterm infants with CLD had a 39% reduction (12.8% placebo *vs* 7.9% palivizumab, $P = 0.038$).

Post-marketing/phase IV data

Pharmacovigilance using large numbers of patients in phase IV trials facilitates the expansion of the efficacy and safety profile of new drugs. Palivizumab received marketing approval by the USA Food and Drug Administration in July 1998 and by the European Commission for Proprietary Medicinal Products in August 1999. Numerous postmarketing/phase IV studies have been conducted to collect additional safety and efficacy data on palivizumab. In the USA, the RSV Education and Compliance Helpline (REACH) program was implemented to enhance parent education about RSV and compliance with monthly prophylaxis.[40] Telephone contacts were made bi-monthly and reported adverse events were collected and monitored for follow-up. Despite active collection of adverse event information, a significantly lower rate of reported serious adverse events (SAE) was observed when compared with the IMpact-RSV trial; total rate of children with one or more SAE was 2.8% for REACH, 29.7% for IMpact-RSV palivizumab group, and 34.0% for IMpact-RSV placebo group. The most common SAE included cough, rhinitis, and lung disorder. The hospitalization rate in this cohort was only 1.5%, which compares favorably to the IMpact-RSV rate of 4.8% in palivizumab recipients.

Outcomes studies were conducted in the USA over two consecutive years in which 12 geographically distinct sites evaluated children less than 2-years-old that had received one or more injections of palivizumab.[41,42] The RSV hospitalization rate in the 1839 and 2830 children studied was 2.3 and 2.4%, respectively. In the second year of this study, 45.6% of the children hospitalized had a history of CLD, 11 (0.4%) required intensive care, and 13 (0.46%) required mechanical ventilation.

An Expanded Access program was conducted in 97 centers in 20 countries around the world where palivizumab was not yet available. The adverse events observed in the 665 children enrolled included mild injection site reaction, fever, diarrhea, nervousness, rhinitis and increased cough; the rate observed was less than or equal to that in the IMpact-RSV palivizumab group.[43]

Conclusion

Respiratory syncytial virus is an important cause of serious lower respiratory tract infection in high-risk infants and young children in Japan. It should be stressed that a major aspect in the prevention of RSV infection in high-risk infants is education of parents and caregivers to reduce exposure and transmission of the virus. Hand washing in all settings, as well as limiting exposure to high-risk settings (e.g. day-care centers) and environmental toxins, such as cigarette smoke, are important preventative measures, particularly during the RSV season. Currently, there is no alternative product to palivizumab for RSV prophylaxis. Palivizumab is currently being considered for licensure for prophylaxis against severe RSV illness in selected high-risk children in Japan.

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