Synagis® Helping Infants and Parents Breathe Easier: A Case Study

November through April are worrisome months for parents of premature infants or children under the age of two with ailments such as chronic lung disease, congenital heart disease or cystic fibrosis for it is the season for Respiratory Syncytial Virus (RSV) infections, which typically necessitates hospitalization for such children.[1, 2] RSV can lead to a serious highly contagious lower respiratory tract disease and is the leading cause of pneumonia and severe sometimes fatal respiratory tract infections in young children.[3] Fortunately, in June 1998, the Food and Drug Administration (FDA) approved a new treatment, Synagis® (palivizumab), a monoclonal antibody produced by recombinant biotechnology, which is specifically designed to neutralize RSV.[2]

Epidemiological Features of RSV

RSV is airborne and can also be spread through physical contact. RSV linked epidemics are seasonal, but their timing depends upon the geographic location.[3] RSV infection is primarily manifest as bronchiolitis or pneumonia. Each year 90,000-125,000 young children through out the United States are hospitalized due to RSV infection.[1, 4] The risk of severe infection and hospitalization increases with risk factors such as premature birth, chronic lung disease, congenital heart disease, immunodeficiency, immunosuppression, passive smoke exposure, day care attendance and birth within 6 months before the RSV season.[1, 2, 4]

Epidemiological Measure	Statistics
Hospitalization[1, 4] (U.S.)	90,000 – 125,000 admissions/year
Prevalence[1]	~100% seropositive by 2 years old
Mortality[5] (worldwide)	~600,000
Morbidity[1, 3] (during RSV season)	50 – 80% bronchiolitis hospitalizations 30 - 60% pneumonia hospitalizations
Demographics[3]	Time of RSV season differs geographically 30% > males vs. females

Management and Prevention of RSV Disease

Once an infant is hospitalized with a severe RSV infection managing the disease is complicated. Treatment involves mechanical removal of secretions, proper positioning of the infant, administration of humidified oxygen, possible respiratory assistance as well as measures to prevent nosocomial infections (infections originating or contracted in a hospital).[3]

To date, the FDA has only approved one antiviral drug, for the treatment of serious RSV infection in hospitalized children. Though recent studies indicated that this therapy has questionable efficacy[6]

Fortunately, products are available to prevent children at risk from experiencing serious RSV infection.

For example, the FDA has approved an intravenously administered therapy (RespiGam®, RSV-IGIV) to prevent severe RSV infections in children under 2 years old with chronic lung disease or that were born prematurely.[6, 7] Given prophylactically, it reduces the frequency and duration of hospitalization for both RSV and non-RSV respiratory infections. However, monthly hospital visits for 4-hour intravenous infusions that must be administered throughout the RSV season.[7] Moreover, since it is a blood product there is a risk of exposing the child to blood-borne pathogens.[8]

Synagis® is a monoclonal antibody that is being used to prevent serious RSV infection in high-risk infants. It can be administered as a shot in the muscle of the thigh in the doctor's office.[2] Additionally, it has fewer adverse side effects, does not interfere with routine vaccinations, and is not a blood product. Due to such positive attributes, Synagis® is recommended by the American Academy of Pediatricians as a RSV prophylaxis. Synagis® is not yet recommended for children with cyanotic congenital heart disease.[7]

For optimal effectiveness, injections must be taken throughout the RSV season since each injection confers 30 days of protection. Patients with severe chronic lung disease may require more than one season of prophylaxis to prevent serious lower respiratory tract RSV infection.[7]

Development of Synagis®

Synagis® is a prime example of how investing in biomedical research improves lives. In 1998, Synagis® became the first monoclonal antibody to be licensed by the FDA and successfully developed for an infectious disease due to the fruitful partnership between the National Institute for Allergy and Infectious Diseases (NIAID) and MedImmune, Inc.[1, 9]

Specific Role of NIH

In the mid 1980s an innovative group of scientists at the NIAID conducted the early stage research that resulted in the derivation of monoclonal antibodies directed against RSV. Below is a description of each group member's unique contribution to the development of murine monoclonal antibodies capable of conferring resistance to RSV infection and disease in experimental animals.[10]

Dr. Peter Collins uncovered the molecular biology of RSV. Once he and Dr. Brian Murphy began collaborating, it became apparent that this would be useful in the production and identification of monoclonal antibodies. Dr. Murphy then designed an immunization scheme to identify and characterize monoclonal antibodies that selectively reacted with the F-glycoprotein. Postdoctoral fellows Dr. van Wyke Coelingh and Dr. Judy Beeler generated monoclonal antibodies and identified four sites on the RSV viron that are important for neutralizing the RSV. Dr. Greg Prince explored the usefulness of antibodies in prophylaxis

R & D Timeline

Antibodies created by NIAID scientists 10/1/85-9/30/86

Article about antibodies published 1989

MTAs signed- NIH provides antibodies to MedImmune 9/6/89 & 1/4/91

MedImmune antibodies humanized 1992

NIH- patent filed on antibodies 12/10/93

MedImmune- preclinical studies 1994

MedImmune- initial preparation of Cell Banks 4/1994

MedImmune-clinical lot production of Synagis® 5/1994

MedImmune- patent filed on humanized antibodies 8/15/1994

Biological License Agreement between MedImmune and NIH 8/23/1994

and treatment of RSV. Thus, he and Dr. Robert Chanock were interested in discovering the therapeutic viability antibodies so conducted numerous animal studies. [10]

Specific Role of MedImmune, Inc.
The relationship between NIH and MedImmune, Inc. began in 1989 when NIAID provided the company with murine monoclonal antibodies directed against RSV via Material Transfer Agreement (MTA).[11] MedImmune scientists began *in vitro* tests using these antibodies along with ones obtained from the Centers for Disease Control.[12]

Realizing the potential use of antibodies to relieve the public health burden RSV disease, the research team set off to develop a human correlate to the lead antibody that binds the virus strongly in a region that can be found in all isolates of the virus in order to effectively prevent infection and spread of the virus. Reaching this goal, which resulted in the development of Syangis®, required a 7-year commitment of financial and human resources on the part of MedImmune, Inc.[13]

As a part of this effort MedImmune, Inc. sponsored and/or participated in preclinical and phase I-III clinical trials to establish the safety, possible side effects, effective dose and tolerance of Synagis, the best way to administer it, as well as how the drug is adsorbed broken down in the body. The pivotal IMpact-RSV multinational patient phase III trial culminated in FDA approval in June 19, 1998 of a Biological License Application for Synagis® for the prevention of RSV infection in infants.[2, 8]

The next major undertaking on the part of MedImmune was to develop a multi-staged process to reliably produce large quantities of identical clinical grade monoclonal antibodies.[14] This necessitates that strict quality controls be maintained. To meet international demand for Synagis®, commercial scale manufacturing was contracted out to Boehringer Ingelheim[13, 14]

Synagis-Related Epidemiology

In the year 2000, over 100,000 patients were treated with Synagis® with the encouraging result of reduced RSV infection and hospitalization of these high-risk infants.[7] As a consequence of its impact on hospitalization rates, Synagis® reduced the number of days an infant must spend in the hospital, the severity of the infection, the need for oxygen treatments, as well as the incidence of admitting the children to the intensive care unit.[8, 15] Furthermore, parents tend to follow the prescribed regimen as indicated by the high rate of compliance.[15]

Epidemiological Measure[16]	Non-prophylaxed	Synagis®-prophylaxed
RSV Hospitalization -CLD* Patients > 2 years old	18.4%	5.6%
-29-32 wG** no CLD	10.3%	2.0%
-22-35 wG no CLD	9.8%	1.5%
RSV outbreak (Infection rate) (Duration)	32% 7 weeks	7.6% 7 days

* CLD= chronic lung disease ** wG= weeks gestation

Public Health Benefit

Synagis is having a major impact upon the public health. It reduces the incidence of RSV hospitalization and eliminates the risk of nosocomial infections or blood borne pathogens. Synagis also improves the patients' quality of life because it is less invasive and can be administered in a doctor's office removing the need for chronically ill or prematurely born infants to return to the hospital.

Synagis is a prime example of how government-industry partnerships benefit the public. The NIAID researchers derived a novel antibody that could prevent RSV infection in cotton rats. However, without the additional research and development conducted by MedImmune, Inc., the therapeutic potential of the antibody for humans would not have been realized. Thus, linking federal laboratories with private corporations allow for the introduction of innovative products to the market place that can be used to improve the public health.

R & D Timeline

14 MedImmune Sponsored Clinical Studies 1994-1997

Clinical Trials Phase I/II Phase III 12/94-4/96 11/96-5/97

MedImmune- phaseIII clinical lot production of Synagis 4/1996

MedImmune files Biologics License Application with FDA 12/19/97

NIH patent #5,762,905 issues for antibodies 6/9/1998

FDA approves Synagis® 6/19/1998

MedImmune- scale up for commercialization 1998

MedImmune patent #5,824,307 issues for humanized antibodies 10/20/1998

First Season in Use 1998-99

References

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