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EXPERT REVIEWS

Hot topics in the prevention of respiratory syncytial virus disease

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7th International Respiratory Syncytial Virus Symposium

2–5 December 2010, Rotterdam, The Netherlands

The 7th International Respiratory Syncytial Virus Symposium took place in Hotel Blijdorp, Rotterdam, The Netherlands. The series has been running since 1996; this meeting took place after a 3-year gap, and was attended by approximately 200 clinicians, scientists and industry representatives from all over the world. The conference covered all aspects of respiratory syncytial virus disease, including virology, cell biology, pathogenesis, clinical presentation, diagnosis, immunology, vaccines, antivirals and other therapeutic approaches. Reviews by invited keynote speakers were accompanied by oral and poster presentations, with ample opportunity for discussion of unpublished work. This article summarizes a small selection of hot topics from the meeting, focused on pathogenesis, therapeutics and vaccine development.

Pathogenesis

Respiratory syncytial virus (RSV) causes acute upper and lower respiratory tract infections, especially in infants. It is the most common cause of bronchiolitis, which is the most frequent single cause of hospital admission in infants. Furthermore, it also causes a significant disease burden and mortality in the elderly. Despite more than 40 years of study, our understanding of the pathogenesis of RSV disease continues to evolve. Extensive research in infected people and animal models has not yet led to commercially available effective antivirals or vaccines, with the exception of palivizumab for immunoprophylaxis in selected high-risk children.

The meeting opened with a discussion of the benefits and drawbacks of animal models, particularly mice. While mice offer a convenient, versatile and well-characterized host, enabling a large number of possible disease mechanisms to be discovered, there are significant limitations. Inbred mice, laboratory-adapted viruses and ultra-clean facilities enable obtainment of rapidly reproducible results, but these conditions are quite different from those that apply during human infections. An interactive cycle of discovery and testing of mechanisms in human and in animal models was proposed and was illustrated by evidence that defective immune regulation may be part of the reason that formalin-inactivated vaccines augment disease (Peter Openshaw, Imperial College London, UK) and that depletion of regulatory T cells disrupts the chemokine gradient that would otherwise draw these effector cells into the lung (Steven Varga, University of Iowa, IA, USA). Kate Stokes (Emory University, GA, USA) added to the complexity of the situation, presenting data on murine infection with a recent clinical isolate of RSV (A2001/2-20) showing that mice infected with this virus suffer more severe disease than those infected with the normal laboratory strain (A2), with higher lung viral antigen titers, enhanced mucin production and higher levels of IL-13 present in the lungs. They ascribed these differences to variation in the viral F protein, since expression of the 2-20F protein in A2 resulted in an enhanced phenotype.

Cell biology

Richard Hegele (University of Toronto, ON, Canada) announced his discovery that nucleolin on the apical surface of human epithelial cells is a major cellular receptor for RSV binding. Nucleolin binding was initially found using viral overlay protein binding studies on multiple cell types, which showed that a single

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protein was responsible for bands in different cell lysates. Soluble nucleolin was found to neutralize RSV, as did anti-nucleolin antibody. Moreover, nucleolin knock-down with siRNA inhibited infection and transfection of human nucleolin into insect cells (lacking surface nucleolin and resistant to RSV infection) restored infectivity. He concluded that this newly identified receptor could be a target for antivirals, but opened his findings to independent confirmation.

Clinical aspects

Ann Falsey (University of Rochester, MN, USA) presented an update on the burden of RSV disease in adults. In the USA, RSV results in 10,000–14,000 deaths and 200,000–400,000 hospitalizations each year in individuals over 65 years of age. Risk factors for admission include older age, comorbidity (e.g., COPD, heart failure) and contact with young children. Diagnosis in this age group is difficult because viral shedding is much lower than that seen in children, making commonly used antigen tests insensitive. The pathogenesis in this age group was characterized by prolonged innate immune responses and a Th2-dominated T-cell response. The fact that those who have RSV disease tend to have low serum neutralizing antibody makes vaccination an attractive strategy for this age group.

James Nokes (Wellcome Trust Research Programme, Kilifi, Kenya) showed that approximately 4500 children are admitted to hospital in Kilifi each year, and that as malaria declined, RSV, rather than rhinovirus, was the main driver of seasonal peaks in admission over the last 8 years. A community-based study looking at RSV transmission within households is ongoing and Nokes argued for the use of RSV vaccines outside the classical risk group of early infancy.

Vaccine development

Formalin-inactivated vaccines were tested in the 1960s with disastrous results – disease severity and hospital admission rates were increased in vaccinees subsequently naturally infected with RSV, and at least two deaths occurred. Fear of inducing pathogenic immunity and the difficulty of designing a safe and effective vaccine for infants (in which the peak of disease occurs at 1–3 months of age) has hampered vaccine development for 40 years. However, progress continues with live-attenuated, virosomal and recombinant vaccines.

Ursula Bucholz (NIAID, MD, USA) gave an update on live-attenuated vaccines (e.g., rA2cp248/404/1030ΔSH, a cold-passaged, *SH*-gene deleted mutant, and a ΔM2-2 virus) and described Phase II studies in seronegative children. Both these live viruses were immunogenic, and reverse genetics has been used to stabilize the mutants and reduce the frequency of reversion to virulence. Julia Hurwitz (University of Tennessee, TN, USA) discussed the use of a recombinant Sendai virus-based RSV vaccine. Sendai virus (a murine parainfluenza virus) can infect humans but does not cause disease, making it an ideal live-vaccine vector, inducing both T- and B-cell memory responses and mucosal immunity. Insertion of the RSV *F* gene into Sendai virus and intranasal inoculation protected African green monkeys from challenge with human parainfluenza virus (PIV)-1 and RSV and was well tolerated in small-scale Phase I human studies. Along similar lines, David Bernstein (Cincinnati Children's Hospital, OH, USA) showed that MEDI-534 (Medimmune, MD, USA), a live-attenuated chimeric bovine/human PIV-3 intranasal vaccine, genetically engineered to express human RSV-F protein, was well tolerated in seronegative children 6–24 months of age. Vaccine take (seroconversion or viral shedding) was dose-dependent, at 67 and 100% for RSV and PIV-3, respectively.

There are also a number of vaccines in preclinical development. Virosomes are virus-sized lipid bilayer vesicles containing surface viral glycoproteins but no nucleocapsid. PEV4 (Pevion Biotech Ltd, Bern, Switzerland) is a virosomal vaccine candidate formulated to contain RSV-F protein; subcutaneous injection of these virosomes into mice induced a potent neutralizing antibody response and mitigated disease following subsequent intranasal challenge with RSV.

Therapeutics

Antiviral therapy for RSV is limited, with ribavirin showing little efficacy. Development of antiviral strategies is therefore paramount, but some assurance that lowering viral load will reduce clinical disease is required. John DeVincenzo (University of Tennessee) showed clinical and mathematical modeling data on the dynamics of viral load and disease in RSV, with an emphasis on the relationship between symptom onset, positivity of available diagnostic tests and natural viral clearance. Viral load appears to follow disease in experimentally infected adults and in naturally infected infants. Rapid diagnostic antigen tests can readily detect the virus in nasopharyngeal secretions of children. The window between symptoms and disappearance of viral load for RSV (5–7 days) is substantially greater than that for influenza (2–3 days), facilitating RSV antiviral intervention.

While palivizumab (an anti-RSV-F monoclonal antibody) is effective for prophylaxis in risk groups, use of antibodies as a therapeutic measure was previously disappointing. Nanobodies are antibody fragments consisting of a single monomeric variable domain. They occur naturally in camels, and RSV-specific nanobodies can be derived by immunization of camels. Erik Depla (Ablynx, Ghent, Belgium) showed that Nb ALX-0171® (Ablynx, NV, USA), a trivalent anti-RSV nanobody consisting of three identical epitopes, was superior to palivizumab in a plaque-reduction assay of a panel of 51 out of 61 recent clinical RSV isolates. Evaluation of Nb ALX-0171 as a therapeutic agent may reveal efficacy of this novel approach.

Severe RSV disease primarily involves the lungs, thus delivery of a therapeutic agent to this site is imperative for efficacy. Robert Cook (MicroDose Therapeutx Inc., NJ, USA) has developed MDT-637, a potent antiviral delivered as a dry powder via a MicroDose inhaler designed to be used in infants, adults and the elderly. MDT-637 has been shown to be 40,000-times more potent in cell culture systems than ribavirin. Evaluation of this inhaler system using the Sophia Anatomical Infant Nose–Throat (SAINT) model, which simulates powder deposition in the

nasopharynx and lung during infant tidal breathing, suggests efficient lung delivery. Aerosol doses were independent of flow rate and a 16-µg dose was shown to reflect a 2-µm drug concentration in simulated lung fluid, approximately 3300-times the IC_{50}. MDT-637 and this method of delivery appear promising as a therapeutic strategy in severe RSV infection.

Conclusion

It is clear that the excellent data we have on the mechanisms of RSV disease from animal models now needs to be confirmed in humans to enable development of antivirals and vaccines, and human challenge studies provide an ideal proof-of-concept model. It is also noteworthy that the target groups for vaccines include not only neonates but also older children, adults with lung disease, caregivers and the elderly. Vaccination of such risk groups may have a significant impact on community and nosocomial transmission, and provide proof of concept for future vaccines directed at pregnant women and their infants.

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