A Review of Therapeutics in Clinical Development for Respiratory Syncytial Virus and Influenza in Children

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ABSTRACT

Purpose: Respiratory syncytial virus (RSV) and influenza are important viral pathogens worldwide. Children, in particular, bear considerable burdens of morbidity and mortality associated with these viruses. There are limited therapeutic options for children infected with RSV or influenza. This review focuses on therapeutics for RSV and influenza that are currently under clinical investigation.

Methods: This study used a systematic approach to identify prospective therapeutics in clinical trials and briefly reviewed those that are currently available for use in adults and children.

Findings: Overall, we found 14 investigational drugs currently in clinical trials for RSV and 20 investigation drugs currently in clinical trials for influenza. These candidates range in development from Phase I to Phase III clinical trials.

Implications: Both RSV and influenza are targets for active therapeutic research, and promising candidates for both viruses are currently in clinical development. (*Clin Ther*. 2018;■:1–14)

Key words: antivirals, influenza, novel, RSV, treatment.

INTRODUCTION

Respiratory viruses significantly affect the health and wellness of pediatric patients worldwide.[1] Since their discovery, respiratory syncytial virus (RSV) and influenza viruses have been the focus of active vaccine development as well as therapeutic investigations.[2] One of the hurdles for the development of vaccines for these viruses is their capacity for reinfection with either the same or differing strains given that natural infection does not elicit lifelong immunity.[2,3] To date, there is no effective vaccine against RSV, and the influenza virus vaccine requires yearly administration and offers imperfect protection.[4] Therefore, therapeutics for both viruses are important to any patient care strategy. However, their development has been difficult, especially because a reduction in viral load does not always correlate with a reduction in symptoms. The present article provides an update on the therapeutic options currently available or in clinical development that could one day be used in children.

MATERIALS AND METHODS

A systematic review of current and developing therapies for both RSV and influenza was performed. The PubMed, MEDLINE (Ovid), and Cochrane databases were used for the review. To identify individual therapeutics, the following search terms were used in each database: "RSV," "Respiratory Syncytial Virus," "Influenza," "Therapy," and "Treatment." The searches were filtered to the last 5 years, human subjects, and patients <18 years of age. In addition, the search terms "Respiratory Syncytial Virus" and "Influenza" were searched in the ClinicalTrials.gov database. All search result citations/entries were then downloaded and reviewed for inclusion based on title. These results (abstracts and manuscripts restricted to the English language) were then reviewed, and a list of therapeutics was created for each virus. A nonsystematic search was also performed to find supplementary data on each therapeutic. Each drug name was entered into PubMed, ClinicalTrials.gov, and the US Food and Drug Administration (FDA) website, and those search

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results were reviewed to include additional data not retrieved in the initial search.

RESULTS

A total of 195 articles were identified that discussed RSV and 357 articles that discussed influenza therapeutics. After duplicates were excluded, 23 RSV and 108 influenza articles were reviewed to build a list of current RSV and influenza therapeutics in clinical trials. This method resulted in a list of 14 investigational drugs for RSV and 20 investigational drugs for influenza in addition to those currently licensed in the United States by the FDA. These results are summarized in Tables I and II.

Respiratory Syncytial Virus

RSV is a single-stranded RNA virus within the pneumovirus family and is ubiquitous worldwide.[2] Primary infection affects almost all children before the second year of life, and re-infection can occur throughout life. In the United States, RSV is estimated to infect 3 per 1000 children aged <5 years and 17 per 1000 children aged <6 months each year.[5] Presentations can range from upper respiratory tract symptoms (congestion and cough) to lower respiratory tract symptoms (bronchiolitis and pneumonia). Approximately one third of infants infected in the first year of life will develop lower respiratory tract illness.[2] Currently, the mainstay of treatment for immunocompetent patients is supportive care, which includes fluid resuscitation and respiratory support. Although therapies such as ribavirin, palivizumab, and intravenous immunoglobulin are sometimes used for immunocompromised patients, their efficacy is uncertain.[6]

Therapeutic Targets

Typically, RSV therapeutics in development have focused on inhibiting viral entry into respiratory epithelial cells or interfering with viral replication.[7] The RSV genome encodes 11 proteins, which are similar between the 2 major strain groups (A and B). Of these proteins, the most commonly used therapeutic target is the fusion (F) protein.[8] The F protein is a viral surface protein that binds to the respiratory epithelial surface, and its inhibition prevents viral fusion and subsequent entry of RSV into the respiratory epithelial cell.

Another common therapeutic target is the RSV nucleocapsid. In RSV, the nucleocapsid comprises 5 different proteins, the nucleo (N)-protein, the phospho (P)-protein, the large polymerase protein (L-protein or RNA polymerase), and regulatory proteins called M2-1 and M2-2.[8] The N, P, and L proteins are all being evaluated as potential therapeutic targets for RSV in clinical trials. Another pathway that indirectly targets the nucleocapsid is the inhibition of nucleocapsid mRNA. This mechanism prevents formation of the nucleocapsid and thus viral replication. What makes both the F protein and the N protein so attractive as targets is that they are both highly conserved and are likely essential for RSV viability.[9] These targets and their associated potential therapeutics are summarized in Figure 1.

FDA-Approved Therapies

To date, the only FDA-approved therapy available for RSV infection is inhaled ribavirin. Ribavirin is a guanosine analogue with broad antiviral activity that includes RSV.[7] The FDA approved an inhaled formulation in 1986 for the treatment of infants and children with RSV bronchiolitis.[10] However, in 2006, the American Academy of Pediatrics recommended against the routine use of ribavirin for immunocompetent infants with bronchiolitis on the grounds that the effectiveness was limited and the potential risks therefore outweighed the benefits in this population.[11] Inhaled ribavirin is still used in selected immunocompromised patients for the treatment of RSV in an attempt to treat or prevent progression to lower respiratory tract illness.[12] Orally administered ribavirin has been suggested as a potential therapy in immunocompromised patients; however, its efficacy has yet to be determined.[13]

Therapies Currently in Clinical Trials

Antibodies

Two potential antibody-based therapies are in Phase II clinical trials (RI-001 and ALX-0171).[14] RI-001 is a polyclonal RSV neutralizing antibody derived from plasma donors with high titers that is indicated for immunocompromised adults and children.[8] A similar formulation, respiratory syncytial virus immune globulin intravenous (RSV-IGIV), was approved by the FDA in 1996 for the prevention of RSV disease in children; however, it was voluntarily discontinued in 2003 after the FDA approval of palivizumab, a monoclonal antibody.[15] Although RSV-IGIV never showed therapeutic benefit in the setting of ongoing RSV infection, the hope was that RI-001 could show efficacy in the immunocompromised population.[15,16] RI-001 was