Expanding the Armamentarium Against Respiratory Viral Infections: DAS181

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(See the major article by Moss et al, on pages 1844–51.)

Respiratory viral infections result in significant morbidity and mortality in adults and children globally. Influenza, alone, is responsible for seasonal epidemics resulting in 3–5 million severe infections and 250,000–500,000 deaths per year [1]. Additionally, influenza results in milder infections which significantly reduce productivity among otherwise healthy adults, resulting in approximately $26.7 billion in direct and indirect costs annually [2]. During the recent influenza A(H1N1) pandemic, influenza was associated with a significant increase in hospitalizations, particularly among individuals <65 years of age and those without co-morbidities, as compared with what is seen in interpandemic years [3]. Furthermore, the pandemic was associated with 284,000 (range, 151,700–575,400) excess deaths [4]. Data from randomized, placebo-controlled studies have documented that antiviral therapy with neuraminidase inhibitors (oseltamivir and zanamivir) and M2 inhibitors (amantadine and rimantadine) reduce the duration of illness attributable to influenza, speed clearance of virus from the host, and reduce infectious and noninfectious complications among otherwise healthy ambulatory adults and children [5, 6]. Furthermore, data from several retrospective studies prior to and during the pandemic consistently demonstrated that antiviral therapy, typically with oral oseltamivir, for adults hospitalized with influenza is associated with more rapid improvement in clinical symptoms, return to usual activity, clearance of viral shedding, and reduction in overall mortality; some studies have also shown a shorter duration of hospitalization and reduced progression to pneumonia and critical illness [7].

Unfortunately, development of antiviral resistance has significantly limited our options in the treatment of influenza. Early after the introduction of M2 inhibitors to clinical practice, emergence of resistance during therapy, as the result of mutations in 1 of 5 commonly recognized sites in the M2 gene, occurred frequently. More recently, M2 resistant variants of influenza A(H3N2) emerged and became established within the viruses circulating globally; in addition, the pandemic influenza A(H1N1) virus, which replaced the seasonal influenza A(H1N1) virus worldwide, is resistant to M2 inhibitors [8]. As a result, most guidelines now recommend against the use of M2 inhibitors for the prevention and treatment of influenza [9]. Resistance to the neuraminidase inhibitors may occur as the result of mutations in the neuraminidase gene, the hemagglutinin gene, or both [10]. Group 1 neuraminidases appear to be more susceptible to the development of oseltamivir resistance, as was seen with the global emergence of oseltamivir resistance in the previous seasonal influenza A(H1N1) virus in 2008–2009 [10]. Given our current reliance on neuraminidases for the management of influenza, oseltamivir resistance emerging globally in the background of M2 inhibitor resistance would greatly limit our options for treatment of influenza. As such, antiviral agents with novel mechanisms of action are clearly needed.

DAS181 is a novel antiviral that consists of a sialidase from Actinomyces viscosus attached to a respiratory epithelium-anchoring domain that is critical for enhancing the efficacy and prolonging retention within the respiratory tract [11]. The drug cleaves the terminal sialic acid residues from the surface of human respiratory epithelial cells, thereby reducing the binding and, therefore, infectivity of influenza A and B viruses as well as parainfluenza viruses (PIV) [11]. Desialylation occurs rapidly and results in an inhibitory effect that lasts, ex vivo, for at least 2 days [11]. In addition, DAS181 appears to be potent against seasonal influenza A and B viruses, the 2009 pandemic influenza A(H1N1) virus, avian influenza A(H5N1) virus, and PIV types.
DAS181 appears to be active against neuraminidase inhibitor-resistant variants of influenza [11]. Limited resistance to DAS181 can be selected in vitro, as the result of mutations in the hemagglutinin and neuraminidase molecules associated with changes in hemagglutinin and neuraminidase function [19]. These variants are unstable and are associated with reduced fitness and small (3–18-fold) increases in EC_{50} [19]. In addition, despite concerns that desialylation of the airway epithelium might lead to increased risk of Streptococcus pneumoniae infections, DAS181 has been shown to decrease the risk of secondary bacterial infections in a murine model [20].

In this issue of the Journal, Moss and colleagues report on the phase II study of DAS181, providing the first clinical insight regarding this novel antiviral against influenza in humans [21]. In this study, 177 adults with laboratory confirmed influenza were randomized to receive DAS181, 10 mg daily for 3 days (multidose), 10 mg as a single dose, or placebo over 3 influenza seasons (2009–2011) in both the Northern and Southern hemispheres; an additional 117 patients were randomized to be treated but did not have documented influenza. The primary endpoint of the study was the change in viral load, as measured by polymerase chain reaction (PCR) using area under the curve (AUC) of pharyngeal wash. There was a statistically significant decrease in viral loads between days 1 and 2 for both DAS181 treatment arms compared with placebo; only the multidose arm resulted in statistically significant superior reduction in viral titers between days 1 and 3 (mean viral load, −1.46 vs −0.73 log_{10} copies/mL) and between days 1 and 5 (mean viral load, −2.38 vs −1.64 log_{10} copies/mL), compared with placebo. Unfortunately, the authors were unable to demonstrate a significant difference in the time to resolution of clinical symptoms, although there was a small but not significant dose-dependent difference in average daily use of acetyaminophen. Overall, the therapy was generally well tolerated, although there were a substantially greater number of adverse events in the multidose and single-dose DAS181-treated patients, compared with placebo-treated patients. There were no differences in FEV_{1} changes with treatment. The most common adverse event was elevation of alkaline phosphatase level, generally without transaminitis, which normalized by the end of the observation period. The clinical significance and pathogenesis of this adverse event clearly warrant further study. There was 1 death of a patient with previously unrecognized human immunodeficiency virus (HIV) infection. In this patient, the influenza viral load improved with treatment but the patient developed pneumonia secondary to Haemophilus parainfluenza and Staphylococcus aureus infection which resulted in her death.

This study is important in that it provides us with useful data to help plan future clinical studies of influenza antivirals. In this study, viral load assessment demonstrated a statistically significant difference between the treatment arms at days 3 and 5 which could not be demonstrated utilizing routine cell culture-based techniques. These data are not surprising since other studies suggest that PCR provides a greater dynamic range and improved sensitivity, particularly at the lower limits of detection [22]. Although there is still controversy about the specific meaning of low-level PCR positivity, molecular methods provide a reliable and robust technology that improves the ability to discern virologic differences between treatment groups. As such, these data provide further evidence that PCR should be considered an important endpoint in influenza antiviral studies, particularly in settings where clinical endpoints have not been validated [22]. Three ongoing studies sponsored by the National Institute of Allergy and Infectious Diseases (ClinicalTrials.gov numbers NCT01052480, NCT01227967, and NCT01314911) will hopefully define the role of virologic endpoints in studies of influenza antivirals while also standardizing and validating virologic endpoints in a range of clinical settings.

This study also highlights the importance of robust assessment of clinical endpoints. The trial assessed the presence and severity, using a 4-point severity scale (0–3), of 7 symptoms commonly associated with influenza: nasal congestion, sore throat, cough, aches and pains, fatigue (tiredness), headache, and chills/sweats (feeling feverish). These symptom assessments are well validated and have been typically utilized in studies of influenza antivirals in ambulatory patients. Most studies to date have collected these clinical data twice daily, along with measured temperature, and have consistently demonstrated a benefit of antiviral therapy, as compared with placebo [22]. In this study, the investigators only assessed symptoms once a day on study days 1, 2, 3, 5, 8, and 14. They did not measure time to resumption of normal activity. Failure to detect a clinical difference in outcomes could be the result of insufficient data or a lack of activity of the therapy. Future studies of this antiviral should assess symptoms at least twice daily, along with assessments of time to resumption of normal activity.

The importance of DAS181 extends beyond influenza, as the agent also has activity against PIV. These viruses are associated with clinically significant disease in transplant patients, particularly hematopoietic stem cell transplant (HSCT) recipients, in whom they may cause significant morbidity and mortality [23, 24]. PIV have also been associated with the development of clinically significant late-onset airflow obstruction in HSCT recipients, and bronchiolitis obliterans syndrome or chronic rejection in lung transplant patients [23, 25, 26]. Unfortunately, to date, no antiviral therapy has proven to have consistent clinical and virologic benefit in the management of PIV infections in solid organ and/or stem cell transplant patients [23, 24]. Two recently published articles suggest that DAS181 holds promise in the management of PIV
infections in transplant patients. One lung and 2 stem cell transplant patients with documented PIV3 infection with clinical and radiologic evidence of lower airway involvement were treated with DAS181 [27, 28]. All 3 patients had improvement in symptoms, oxygenation, pulmonary function, and nasopharyngeal viral loads [27, 28].

Taken together, the data from the phase II study in influenza-infected ambulatory adults and the 3 case reports of PIV-infected transplant patients suggest that DAS181 holds promise for the management of these 2 important respiratory viral infections. Further studies are clearly needed, and such studies should include robust clinical and virologic endpoints. Additionally, DAS181 in combination with other available antivirals should be studied to determine whether such combinations are associated with improved clinical and virologic outcomes and whether the combinations prevent or reduce the emergence of antiviral-resistant variants.

Notes

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References