Creeping toward Effective Antiviral Agents for RSV Infection

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Infection with respiratory syncytial virus (RSV), the cause of annual winter epidemics of respiratory illness in all age groups, is best recognized for being the leading diagnosis in very young infants who are hospitalized.[1] The recent licensure of an RSV prefusion fusion protein (preF) vaccine to be administered during pregnancy and a long-acting preF monoclonal antibody for all newborns proximate to their first RSV season will, it is hoped, reduce hospitalizations.[2,3] Nevertheless, the need remains for an effective antiviral agent to treat infants and older children who are ineligible for or do not benefit from these new interventions.

Aerosolized ribavirin, a nucleoside analogue licensed in 1985, is the sole antiviral agent that has been approved for the treatment of hospitalized infants with RSV infection, but marginal clinical benefit and lingering concerns about toxic effects and cost have curtailed its use except in those with severe immunosuppression.[4] Several small molecules that impede fusion protein–mediated RSV cell entry have satisfactory preclinical properties, including those seen in RSV challenge studies involving humans, but data from phase 3 trials involving infants have been limited.

In this issue of the *Journal*, investigators in China report the results of a two-part, phase 3, double-blind, randomized, placebo-controlled trial of ziresovir, an orally bioavailable fusion inhibitor, in infants 1 to 24 months of age who were hospitalized with RSV infection.[5] Part 1 assessed safety in 54 infants who had been randomly assigned in a 2:1 ratio to receive ziresovir or placebo every 12 hours for 5 days. When no safety signals were identified, 256 additional infants underwent randomization, with the primary end point of differential clinical improvement in the Wang bronchiolitis clinical score (bronchiolitis score) at 48 hours and the key secondary end point of the reduction in the nasal viral load at 96 hours.

After adjustment for the baseline bronchiolitis score, participant age, and illness duration, the decrease (indicating improvement) in the bronchiolitis score at 48 hours was 30% greater in the ziresovir group than in the placebo group, a significant difference. The nasal viral load decreased more rapidly with ziresovir treatment than with placebo, although the between-group difference at 96 hours was modest, at −0.7 $\log_{10}$ copies per milliliter. An important subgroup analysis that was limited to participants 6 months of age or younger showed a significant clinical improvement with ziresovir as compared with placebo. In addition, the proportion of infants with a reduction of at least 75% in the bronchiolitis score at 48 hours favored the ziresovir group. Finally, evidence of drug resistance emerged in 9% of the treated participants, but importantly, viral rebound was not observed. Overall, the results are encouraging, and further studies of ziresovir in more diverse settings and populations are warranted.

So, can we translate the reduction in a clinical severity score (the Wang bronchiolitis clinical score), on a scale that is not fully validated, to clinically relevant outcomes? The mean hospital stay among infants with RSV infection in the United States is generally 2 to 3 days, and thus, whether the measured clinical improvement will result in other clinical benefits, such as earlier hospital discharge, a reduction in discharge home with the receipt of supplemental oxygen, or limited transfer to the pediatric intensive care unit after admission, needs to be determined.

An important consideration in the design of a trial of an RSV antiviral agent is likely to be the effect of timing of the intervention. In this trial, the median time from symptom onset to the first dose of ziresovir or placebo was 4 days, a time when the viral load is already declining.[6] Existing data suggest that illness severity is driven by the early virus-induced host inflammatory response, which is associated with a delayed

innate interferon response, and not necessarily by the viral load, at least as measured in nasal tissue.[7] Antiviral agents to treat influenza are most effective in infants and adults when administered within 48 hours after symptom onset, and the same may be true for RSV infection.[8] If so, inflammatory responses and severity may be better muted by earlier treatment. One study showed that approximately half of hospitalized infants had a health care contact in the 24 hours before admission.[9] Although this approach is not without considerable challenges, it may be possible to begin treatment at these earlier outpatient interactions, especially in the youngest infants or those with prematurity, who are at the highest risk for hospitalization. In addition, early treatment may benefit children 2 to 5 years of age who have underlying high-risk conditions that could lead to hospitalization.[1] Another study population to consider are infants with RSV infection who are seen in emergency departments, given that a substantial proportion of them, if sent home, will return within 24 hours for admission.[10]

Finally, and not inconsequentially, if the positive results reported in this trial are confirmed, they may portend clinical benefits in persons with severe immunosuppression, a group in dire need of an effective RSV antiviral agent. Thus, ziresovir offers the potential to augment the recently approved maternal vaccination and monoclonal antibody approaches for reducing the burden of RSV infection in infants.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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