CB-012 - A Novel Antiviral-Fc Conjugate for Prevention and Treatment of Influenza Virus


Background

The World Health Organization has estimated up to 650,000 influenza-related respiratory deaths annually. In the U.S., the 2017-2018 flu season was one of the most severe in recent history, causing 18,000 people and 80,000 deaths.

While even healthy people are at risk of infection with seasonal flu, certain populations are particularly vulnerable and have higher risk of serious complications - young children, the elderly (people aged >65 years), pregnant women, people with chronic illness (e.g., diabetes, asthma, heart disease), and the immunocompromised. Influenza vaccine effectiveness is only 40%, and current treatment approaches have limitations.

Cidara Therapeutics is using its Cloudbreak platform to develop a novel class of potent, broad-spectrum antiviral agents (AVCs) against influenza that, in a single molecule, combine a surface-acting antiviral agent (targeting mostly TM) with the Fc domain of a human IgG1 antibody (Fig. 1). AVCs function by inhibiting viral replication while simultaneously engaging the immune system, providing a multimodal mechanism of action.

Methods

Prophylactic Efficacy

Lethal mouse influenza models (A/Texas/36/91 [H1N1] and A/Hong Kong/168 [H3N2]) were used to evaluate prophylactic efficacy in vivo. In the H1N1 model (n=10/cohort), a single iv dose of CB-012 (0.4-50 mg/kg) was evaluated when administered 4 hours prior to infection and when administered 28 days prior to infection. In the H3N2 model (n=10/cohort), a single iv dose of CB-012 (0.4-2 mg/kg) was administered 4 hours prior to infection. Efficacy was compared with that of oseltamivir 20 mg/kg orally twice daily (BID) for 5 days starting 8 hours post-infection and with controls. Survival and body weights were monitored for 14 days.

Treatment Efficacy

CB-012 treatment efficacy was evaluated in vivo using a lethal mouse influenza model infected with A/Texas/36/91 (H1N1) virus (n=10/cohort). A single iv dose of CB-012 (1.0 mg/kg) and oral oseltamivir 20 mg/kg BID for 5 days were administered starting 8-8.5 hours post-infection. Survival was monitored for 14 days.

Results

CB-012 demonstrated a long duration of action in mice, where one 2.5 mg/kg dose 28 days prior to infection (A/Texas/36/91 [H1N1]) demonstrated 100% protection from death (Fig. 4) while maintaining similar body weight compared to uninfected controls (data not shown).

In short-term prophylaxis (4 hours prior to infection: A/Texas/36/91 [H1N1], A/Hong Kong/168 [H3N2]; a single 0.4 mg/kg dose of CB-012 demonstrated 100% protection against influenza (Fig. 4) while maintaining similar body weight compared to uninfected controls (data not shown).

Figure 4. In vivo Prophylactic Efficacy of Single Dose CB-012 Against Influenza (A) A/Texas/36/91 (H1N1) and (B) A/Hong Kong/168 (H3N2) Compared with Oseltamivir BID x 5 days.

Conclusions

• CB-012 demonstrated potent activity against seasonal and pandemic influenza A strains and influenza B.
• CB-012 inhibited viral growth more efficiently than oseltamivir in vitro.
• Potent CB-012 in vitro activity translated to efficacy in lethal prophylactic and treatment influenza mouse models with a single dose.
• CB-012 displayed extended systemic exposure in mice that translated to long duration of action and efficacy in prophylaxis models.
• These findings with CB-012 validate the multimodal approach of Cloudbreak AVCs for the prevention and treatment of influenza.

References


Acknowledgements

Editorial support was provided by T. Chung (SorinBiotech GmbH) and funded by Cidara Therapeutics, Inc.