

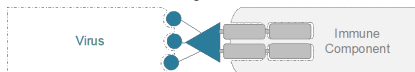
Evaluation of CD377, a Novel Antiviral Fc-Conjugate (AVC), In Vitro Activity and In Vivo Efficacy in Immune-Competent and -Deficient (SCID) Lethal Mouse Models

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INTRODUCTION

Cidara Therapeutics is developing a new generation of antivirals that couple potent, small molecule antiviral agents to the Fc domain of human IgG1 antibodies (Fig. 1). These long-acting, antiviral Fc-conjugates (AVCs) have potent antiviral activity and have the potential to engage the immune system. The long half-lives and potent, intrinsic antiviral activities of AVCs make them well suited for use as preventative agents even in patients with significant immunodeficiencies. CD377 is a development candidate with broad-spectrum influenza A/B coverage undergoing evaluation for use in both immune-competent and -deficient populations.

Figure 1. CD377 comprises a stable conjugate of multiple copies of a surface-acting antiviral agent with the Fc domain of human IgG1



| Targeting moiety | Fc moiety |
|---|---|
| Binds conserved surface target Direct antiviral activity | Provides prolonged half-life Immune engagement potential |

METHODS

CD377 and comparators (oseltamivir, zanamivir, and baloxavir marboxil) were evaluated in vitro by neuraminidase inhibition (NAI) and cytopathic effect (CPE) assays. The pharmacokinetics (PK) and efficacy of CD377 were determined in immune-competent (BALB/c) and immune-deficient (BALB/c SCID) mice.

METHODS (cont.)

Efficacy was assessed by intranasal challenge at 3x the LD₅₀ of influenza A/Puerto Rico/8/1934 (H1N1), followed by a single subcutaneous (SC) dose of CD377, 2 hours post-challenge. The SCID study also evaluated the efficacy of baloxavir at 3 mg/kg (BID x 1 day). Body weights (BW) were monitored for 21 days, with 20% BW loss recorded as mortality.

RESULTS

CD377 demonstrates potent in vitro activity (Table 1). The TM of CD377 is a neuraminidase inhibitor, therefore its activity was assessed in an NAI assay compared to oseltamivir and zanamivir. All 3 had similar activity with IC₅₀ values in the low nM range, and within ~3-fold of each other. However, in a CPE assay which included baloxavir, CD377 was ~5-fold more active than baloxavir and >1,800-fold more active than oseltamivir or zanamivir.

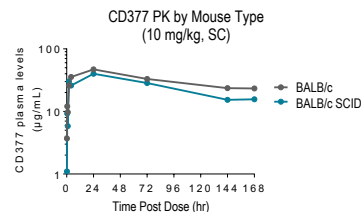
Table 1. In vitro activity of CD377 and comparators.

| Assay Type | In vitro Activity Against A/Puerto Rico/8/34 (H1N1) (nM) | | | |
|-------------------------|--|-------------|-----------|-----------|
| | CD377 | Oseltamivir | Zanamivir | Baloxavir |
| NAI (IC ₅₀) | 1.7 | 1.3 | 0.5 | na |
| CPE (EC ₅₀) | 0.782 | 1460 | 7580 | 3.69 |

CD377 displays comparable PK profiles in immune-competent and immune-deficient mice (Fig. 2). CD377 administered SC to immune-competent and -deficient mice at 10 mg/kg demonstrated similar PK profiles. The PK profiles demonstrate 24-hour distribution followed by shallow elimination. CD377 plasma levels remained high (~20 µg/ml) relative to C_{max} levels over the one-week course of the study.

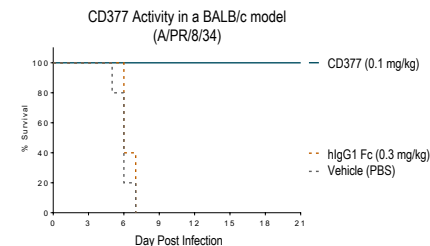
RESULTS (cont.)

Figure 2. Pharmacokinetics of CD377 in BALB/c and BALB/c SCID mice.



CD377 is effective in preventing mortality in immune-competent mice challenged with a lethal dose of influenza A (H1N1), using a single, low SC dose (Fig. 3). In vivo activity of CD377 was determined in wild-type BALB/c mice. Animals administered CD377 two hours post viral challenge were fully protected at doses as low as 0.1 mg/kg in a 3-week study. Mice receiving Fc only or vehicle were not protected.

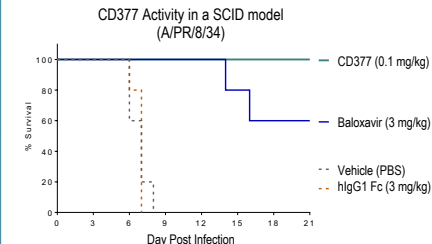
Figure 3. CD377 efficacy in a lethal model of influenza A (H1N1) in immune-competent BALB/c mice.



RESULTS (cont.)

CD377 demonstrates long-lasting protection in a severe model of immunodeficiency (Fig. 4). SCID mice receiving a single IM dose of CD377 as low as 0.1 mg/kg were fully protected for 3 weeks. In contrast, vehicle and Fc-only groups were not protected.

Figure 4. Survival of SCID mice lethally challenged with influenza A.



CONCLUSIONS

The potent, intrinsic antiviral activity of CD377 is sufficient to protect mice against lethal influenza infection, even in a severely immunodeficient background, at doses identical to those required to protect immune-competent mice.

This study underscores the potential of CD377 for prevention and treatment of influenza in immune-senescent and immune-compromised populations.

ACKNOWLEDGMENTS

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