INTRODUCTION

AVCs (antiviral Fc-conjugates) are long-acting, immunotherapeutic conjugates of potent antiviral agents coupled with the Fc domain of human IgG1. CD377 is a novel AVC development candidate for the prevention and treatment of influenza. Here we evaluated CD377 activity when administered by different dosing routes, and by efficacy against the predominant oseltamivir resistance mutation.

CD377 comprises a stable conjugate of multiple copies of a surface-acting neuraminidase inhibitor with the Fc domain of human IgG1.

METHODS

Studies were conducted in BALB/c mice challenged intranasally at 3x the LD₉₅ with oseltamivir-sensitive (A/California/07/2009) or oseltamivir-resistant (A/Texas/23/2012 H275Y and A/Perth/261/2009 H275Y) influenza A (H1N1) strains. A single dose of CD377 (0.1, 0.3, or 1 mg/kg) was administered intravenously (IV), subcutaneously (SC), or intramuscularly (IM) 2 hours post-challenge. Oseltamivir was dosed orally (PO) at 20 mg/kg twice daily, for 5 days. Body weights (BW) and health scores were monitored daily, with ≥20% BW loss recorded as mortality.

RESULTS

Potency of CD377 by dose route (Figures 1 and 1b). Dose route versatility has important implications in hospital or outpatient settings. Therefore, the efficacy of CD377 was determined in a side-by-side study comparing IV, IM, and SC dosing routes. With mortality as the endpoint, all dose routes were equipotent, with full protection achieved with a single 0.1 mg/kg administration of CD377 (Fig 1).

BW was monitored in the above dose route study as a more sensitive determinate of potency based on administration route (Fig. 1b).

Similar to the results of the survival analysis, no statistically significant difference was observed when BW was the endpoint (P=0.38). Collectively, both endpoints indicate equivalent potency of CD377 by all tested dose routes.

RESULTS (CONT’D)

Activity of CD377 against oseltamivir-resistant isolates (Figures 2 and 3). H275Y is the predominant neuraminidase mutation conferring resistance to oseltamivir. As CD377 also inhibits neuraminidase activity, its potency against this mutation was determined in mouse efficacy studies. As expected, a total oseltamivir dose of 200 mg/kg (2x the humanized dose) was not protective against an H1N1 subtype harboring H275Y (Fig. 2). In contrast, CD377 was fully protective against lethal challenge with a single 0.3 mg/kg dose (SC). BW loss at this dose was transient and all animals recovered their starting weight by study end (data not shown).

The susceptibility of the H275Y mutation to CD377 was confirmed in a second isolate with a different genetic background (A/Perth/261/2009). Against this isolate, a single 0.3 mg/kg dose of CD377 was again fully protective while oseltamivir was not (Fig. 3). Although both molecules target neuraminidase, the retention of potency against H275Y by CD377 illustrates its unique activity and mechanism of action compared to oseltamivir.

CONCLUSIONS

• CD377 was equipotent by all tested dose routes, highlighting the potential for SC or IM dosing in outpatient settings.
• A single 0.3-mg/kg dose of CD377 fully protected mice challenged with the clinically relevant H275Y oseltamivir-resistant mutant.
• These data support the development of CD377 for treatment and prevention of influenza.

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