J Antimicrob Chemother. 2010 Aug;65(8):1733-41. Epub 2010 Jun 9.

ASP2151, a novel helicase-primase inhibitor, possesses antiviral activity against varicella-zoster virus and herpes simplex virus types 1 and 2.

Chono K, Katsumata K, Kontani T, Kobayashi M, Sudo K, Yokota T, Konno K, Shimizu Y, Suzuki H.

Source: Drug Discovery Research, Astellas Pharma Inc., Tokyo, Japan.

Abstract

OBJECTIVES: To evaluate and describe the anti-herpesvirus effect of ASP2151, amenamevir, a novel non-nucleoside oxadiazolylphenyl-containing herpesvirus helicase-primase complex inhibitor.

METHODS: The inhibitory effect of ASP2151 on enzymatic activities associated with a recombinant HSV-1 helicase-primase complex was assessed. To investigate the effect on viral DNA replication, we analysed viral DNA in cells infected with herpesviruses [herpes simplex virus (HSV), varicella-zoster virus (VZV) and human cytomegalovirus]. Sequencing analyses were conducted on an ASP2151-resistant VZV mutant. In vitro and in vivo antiviral activities were evaluated using a plaque reduction assay and an HSV-1-infected zosteriform-spread model in mice.

RESULTS: ASP2151 inhibited the single-stranded DNA-dependent ATPase, helicase and primase activities associated with the HSV-1 helicase-primase complex. Antiviral assays revealed that ASP2151, unlike other known HSV helicase-primase inhibitors, exerts equipotent activity against VZV, HSV-1 and HSV-2 through prevention of viral DNA replication. Further, the anti-VZV activity of ASP2151 (EC(50), 0.038-0.10 microM) was more potent against all strains tested than that of aciclovir (EC(50), 1.3-27 microM). ASP2151 was also active against aciclovir-resistant VZV. Amino acid substitutions were found in helicase and primase subunits of ASP2151-resistant VZV. In a mouse zosteriform-spread model, ASP2151 was orally active and inhibited disease progression more potently than valaciclovir.

CONCLUSIONS: ASP2151 is a novel herpes helicase-primase inhibitor that warrants further investigation for the potential treatment of both VZV and HSV infections.

PMID: 20534624