J Antimicrob Chemother. 2007 Aug;60(2):274-9. Epub 2007 Jun 4.

Detection of HSV-1 variants highly resistant to the helicase-primase inhibitor BAY 57-1293 at high frequency in 2 of 10 recent clinical isolates of HSV-1.

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Abstract

OBJECTIVES: BAY 57-1293 is a helicase-primase inhibitor (HPI) from a new class of antivirals that are highly efficacious in herpes simplex virus (HSV)-1 animal infection models. Resistant mutants with point mutations in the helicase (UL5) were reported to be present in laboratory isolates at a low frequency of approximately 10(-6). In contrast, we have shown elsewhere that some laboratory isolates contain resistant variants at higher frequency (10(-4)). Therefore, we screened 10 recent clinical isolates of HSV-1 for BAY 57-1293-resistant virions.

METHODS: Clinical isolates were screened by a plaque reduction assay in Vero cells to determine the frequency of occurrence of BAY 57-1293-resistant variants. The helicase gene for the resistant variants was sequenced.

RESULTS: One isolate contained highly resistant variants at 10(-4) and another at 10(-5). Both variants contained a previously reported BAY 57-1293 resistance mutation (K356N) in UL5 and were >5000-fold resistant.

CONCLUSIONS: Occurrence of HPI-resistant viruses at high frequency in a clinical isolate is intriguing. Two alternative hypotheses are proposed to explain this phenomenon. It is also surprising that two unrelated clinical isolates contain an identical HPI resistance mutation. These results have important implications for HPI drug-resistance monitoring during subsequent clinical trials.

PMID: 17550887 [PubMed - indexed for MEDLINE]