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In search of effective anti-HHV-6 agents

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Abstract

Since HHV-6, like HCMV, is a β-herpesvirus, anti-HCMV drugs such as (val)ganciclovir, foscarnet and cidofovir may, by extrapolation, be advocated for the treatment of HHV-6 infections. At present, no prime candidate for the treatment of HHV-6 infections has been identified or even proposed, which means that the search for antiviral drugs effective against HHV-6-associated diseases should be encouraged. In essence, this search is going into two directions: nucleoside and non-nucleoside analogues. To the first category belong S2242, an N7-substituted purine acyclic derivative; A-5021, a cyclopropyl nucleoside analogue; cyclopropavir, a methylene cyclopropane analogue; lipophilic ester prodrugs of the acyclic nucleoside phosphonate cidofovir; and various other "old" and "new" acyclic nucleoside phosphonate analogues including those derived from the 2,4-diaminopyrimidine (DAPy) skeleton. To the non-nucleoside category belong a number of quinoline-3-carboxamide, aryl sulfone, benzimidazole riboside and phenylenediamine sulfonamide derivatives which could be further optimized from a structure–activity relationship (SAR) viewpoint so as to specifically target HHV-6 replication. Also, specific protein kinase inhibitors may be pursued as anti-HHV-6 agents, a representative example being the compound CMV423 which, being inhibitory to (cellular) protein tyrosine kinases, exhibits potent and selective activity against HHV-6.

Keywords: HHV-6; anti-HHV-6 agents; Nucleoside analogues; Nucleotide analogues; Non-nucleoside analogues; CMV423

1. Introduction

In the search for effective anti-HHV-6 agents, an apparent class of compounds which could be entertained as potentially valuable for the treatment of HHV-6 infections are those antiviral drugs which have already been licensed for use in the treatment of infections due to human cytomegalovirus (HCMV), which, like HHV-6 and HHV-7, belongs to the β-herpesviruses. Licensed anti-HCMV drugs include ganciclovir [9-(1,3-dihydroxy-2-propoxymethyl)-guanine, Cymevene®, Cytovene®] (Fig. 1), its oral produg valganciclovir [L-valine ester of ganciclovir (VGCV), Valcyte®] (Fig.-2), foscarnet [trisodium phosphonoformate, foscarnet sodium, Foscavir®] (Fig. 3), and cidofovir [(*S*)-1-(3-hydroxy-2-phosphonylmethoxy-propyl)cytosine, HPMPC, Vistide®] (Fig. 4).

In addition to the anti-herpesvirus agents which have been specifically licensed as anti-HCMV drugs, the gold standard of the anti-herpesvirus [herpes simplex virus (HSV)] agents, acyclovir [aciclovir (ACV), acycloguanosine, 9-[(2-hydroxyethoxy)methyl]guanine, Zovirax®] (Fig. 5) and its oral prodrug, valaciclovir [L-valine ester of acyclovir (VACV), Zelitrex®, Valtrex®] (Fig. 6) could be considered as potentially valuable in the treatment of HHV-6 infections.

From a comparative evaluation of the *in vitro* activity of acyclovir, ganciclovir, cidofovir and foscarnet against HHV-6, cidofovir appeared to be the most potent, and also the most selective, at least when tested against HHV-6 (type A) in cord blood lymphocytes (Table 1) (De Bolle et al., 2004). When tested against HHV-6 (type A or B) in T-cell lines, the highest selectivity score of the four compounds was achieved by foscarnet.

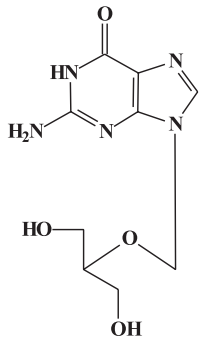

Fig. 1. Ganciclovir [9-(1,3-dihydroxy-2-propoxymethyl)guanine, Cymevene®, Cytovene®].

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Table 1
Anti-HHV-6 activity of acyclovir (ACV), ganciclovir (GCV), cidofovir (CDV), foscarnet (PFA) and CMV423[a]

Assay	HHV-6 strain (variant)	EC_{50} (μM)					SI				
		ACV	GCV	CDV	PFA	CMV423	ACV	GCV	CDV	PFA	CMV423
Cord blood lymphocytes											
DNA hybridization	GS (A)	10	5.8	0.56	9.5	0.017	28	17	182	68	>1765
T-cell lines: HSB-2, MOLT-3											
DNA hybridization	GS (A)	180	32	90	16	0.053	4	<2	3	78	2717
	Z29 (B)	185	69	9.8	25	>100	1	<1	6	40	–

[a] Abbreviations: EC_{50}: 50% (antivirally) effective concentration; SI: selectivity index, or ratio of CC_{50} (50% cytotoxic concentration) to EC_{50}. Data taken from De Bolle et al. (2004).

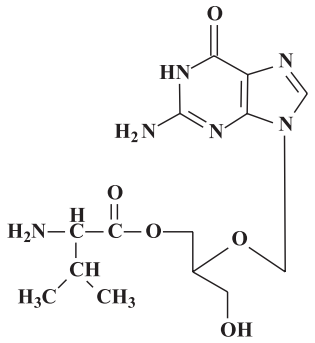

Fig. 2. Valganciclovir [L-valine ester of ganciclovir (VGCV), Valcyte®].

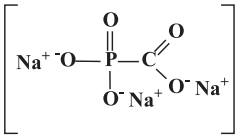

Fig. 3. Foscarnet [trisodium phosphonoformate, foscarnet sodium, Foscavir®].

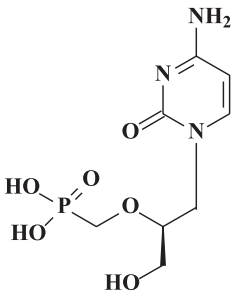

Fig. 4. Cidofovir [(*S*)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine, HPMPC, Vistide®].

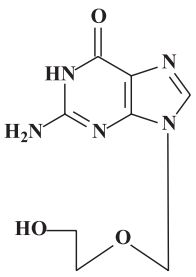

Fig. 5. Acyclovir [Aciclovir (ACV), acycloguanosine, 9-[(2-hydroxyethoxy)methyl]guanine, Zovirax®].

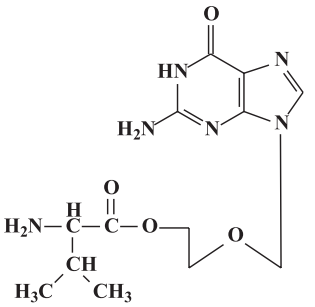

Fig. 6. Valaciclovir [L-valine ester of acyclovir (VACV), Zelitrex®, Valtrex®].

2. Nucleoside/nucleotide analogues

Besides the aforementioned compounds (acyclovir, ganciclovir, cidofovir and foscarnet), some nucleoside analogues, in particular S2242 [2-amino-7-[(1,3-dihydroxy-2-propoxy)methyl]purine] (Fig. 7), A-5021 [(1'S,2'R)-9-[[1',2'-bis(hydroxymethyl)cycloprop-1′-yl]methyl]guanine] (Fig. 8) and cyclopropavir (CPV, ZSM-I-62) (Fig. 9) may yield promise as potential anti-HHV-6 agents. S2242 was found to inhibit HHV-6(A) replication in HSB-2 T-lymphoblasts at an EC_{50} of 0.005 μg/mL (SI = 40) and in human cord blood lymphocytes at an EC_{50} of 0.01 μg/mL (SI ⩾ 100) (De Clercq et al., 2001). A-5021 inhibited HHV-6(A) replication in HSB-2 T-lymphoblasts at an EC_{50} of 3.5 μg/mL (SI = 14) and in human cord blood lymphocytes at an EC_{50} of 0.4 μg/mL (SI = 250) (De Clercq et al., 2001). Cyclopropavir inhibited HHV-6(A) replication in HSB-2 T-lymphoblasts at an EC_{50} of 7.8μM and HHV-6(B) replication in cord blood lymphocytes at an EC_{50} of 0.7μM, while its 50% cytotoxic concentration (CC_{50}) in human foreskin fibroblast (HFF) cultures was >360μM (Kern et al., 2005; Zemlicka, 2006).

The nucleotide analogues that would seem worth pursuing for their potential anti-HHV-6 activity include the oral prodrug forms of cidofovir, hexadecyloxypropyl-cidofovir (HDP-CDV) and octadecyloxyethyl-cidofovir (ODE-CDV) (Fig. 10) (Painter and Hostetler, 2004). These oral prodrugs of cidofovir could be useful in the oral treatment of