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Commentary

Dancing with chemical formulae of antivirals: A personal account

Erik De Clercq *

Rega Institute for Medical Research, KU Leuven, Minderbroedersstraat 10, B-3000 Leuven, Belgium

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GS-9191, GS-9219, cPrPMEDAP, and PMEG
O-DAPy and 5-azaC phosphonate analogues
HEPT and TIBO derivatives
Bicyclam (AMD3100) derivatives

ABSTRACT

A chemical structure is a joy forever, and this is how I perceived the chemical structures of a number of antiviral compounds with which I have been personally acquainted over the past 3 decades: (1) amino acid esters of acyclovir (i.e. valaciclovir); (2) 5-substituted 2′-deoxyuridines (i.e. brivudin); (3) 2′,3′-dideoxynucleoside analogues (i.e. stavudine); (4) acyclic nucleoside phosphonates (ANPs) (i.e. cidofovir, adefovir); (5) tenofovir disoproxil fumarate (TDF) and drug combinations therewith; (6) tenofovir alafenamide (TAF, GS-7340), a new phosphonoamidate prodrug of tenofovir; (7) pro-prodrugs of PMEG (i.e. GS-9191 and GS-9219); (8) new ANPs: O-DAPy and 5-aza-C phosphonates; (9) non-nucleoside reverse transcriptase inhibitors (NNRTIs): HEPT and TIBO derivatives; and (10) bicyclam derivatives (i.e. AMD3100).

1. Introduction

The dawning of the antiviral drug era started now more than 50 years ago, in 1959, with the synthesis of 5-iodo-2′-deoxyuridine (IDU, idoxuridine) [1], the development of a plaque inhibition test for detection of DNA virus inhibitors [2,3], the announcement of the antiviral activity of arabinosyladenine (ara-A, vidarabine, adenine arabinoside) [4], demonstration of the antiviral action of 5-trifluoromethyl-2′-deoxyuridine (TFT, trifluorothymidine) in herpes simplex keratitis [5], demonstration of the antiviral activity (against influenza A) of 1-adamantanamine (amantadine) [6], description of the antiviral activity (against orthopoxviruses) of 1-methylisatin 3-thiosemicarbazone (methisazone) [7], and description of the broad-spectrum antiviral activity of virazole (ribavirin) [8]. Rich Whitley et al. were the first to initiate systemic antiviral therapy (with adenine arabinoside) in the treatment of virus infections (i.e. herpes zoster) in man [9]. Of pivotal importance for the antiviral drug era was the advent in 1977–78 of acyclovir, the first truly specific antiviral drug [10,11].

2. Valaciclovir (Fig. 1)

In the original paper describing the antiviral activity of acyclovir [acycloguanosine, 9-(2-hydroxyethoxymethyl)guanine] [11], it was stated that the program leading to the synthesis of acycloguanosine was initiated after earlier studies had shown that the intact cyclic carbohydrate moiety was not necessary to mimic nucleoside binding to enzymes [12]. That acycloguanosine, the prototype of the acyclic nucleoside analogues, would specifically interact with the thymidine kinase (TK) of HSV, and to a lesser extent, VZV, and thus exert its selective action as an antiherpetic agent (10), could not be predicted, and could therefore be considered as a serendipitous discovery. Acyclovir would, later on, become the "gold standard" (Zovirax®) for HSV therapy [13].

Acyclovir is relatively insoluble in aqueous medium: to increase its aqueous solubility we synthesized the amino acid (i.e. glycine, alanine) esters of acyclovir [14]; for the treatment of HSV keratitis the glycyl ester of acyclovir could be administered as eye drops, whereas the parent compound, acyclovir, had to be applied as eye ointment. Of all the amino acid esters of acyclovir that were synthesized, the valine ester showed the greatest oral bioavailability, and valaciclovir (Valtrex®, Zelitrex®) then replaced acyclovir for the oral treatment of HSV and VZV infections [15]. Inspired by the strategy followed for valaciclovir, ganciclovir (Cytovene®), for the treatment of CMV infections, has also been replaced by its valine ester, valganciclovir (Valcyte®) [16], and, again, the same strategy was followed for the conversion of Cf1743 to FV-100, as further described in Section 2.

Antivirally active acyclic guanosine analogues, such as acyclovir, are first phosphorylated by the virus-encoded thymidine kinase (TK) to the monophosphate (ACV-MP), which is successively phosphorylated to the diphosphate (ACV-DP) by GMP kinase and

* Tel.: +32 26 337367; fax: +32 16 337340.
E-mail address: erik.declercq@rega.kuleuven.be

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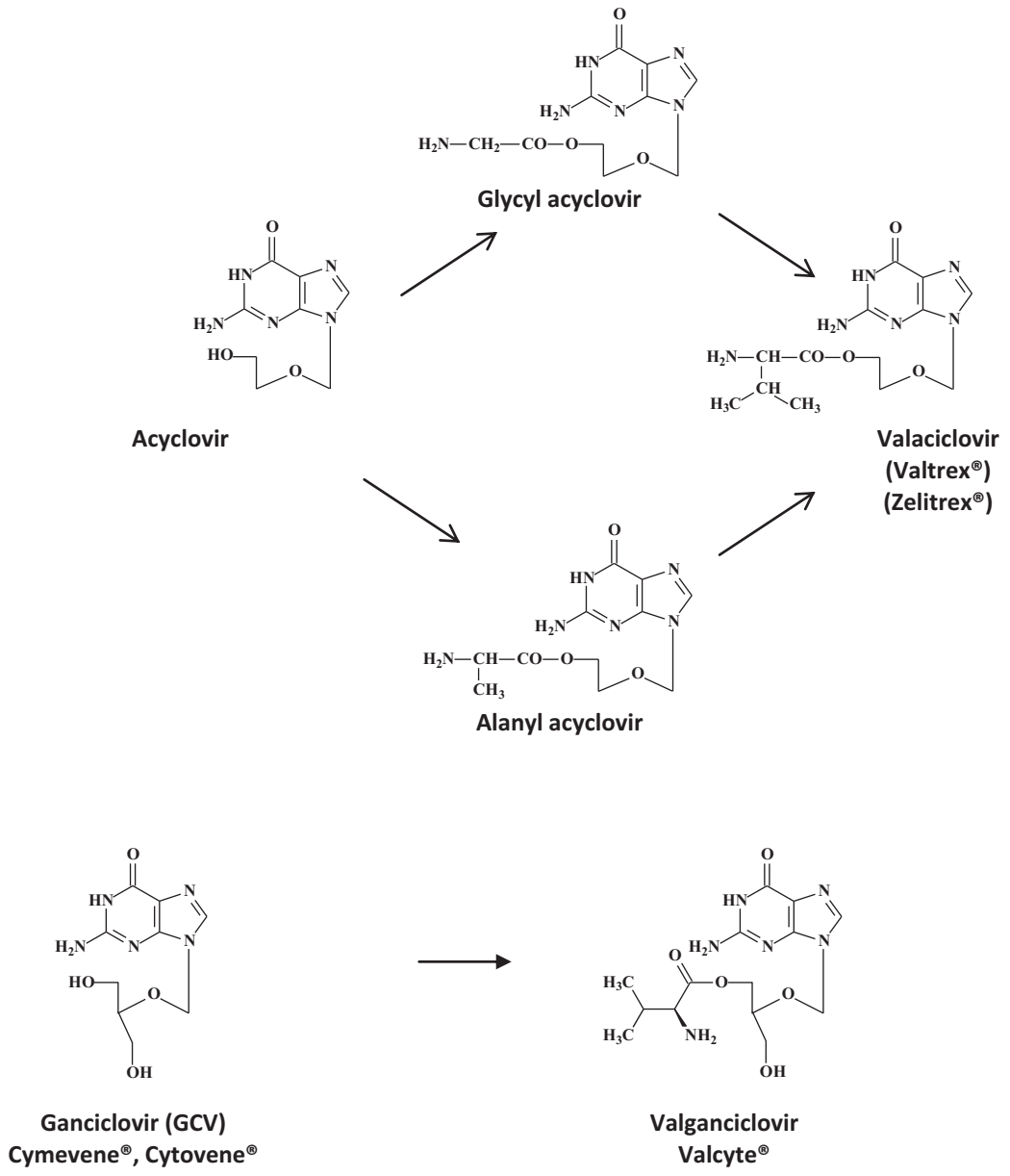

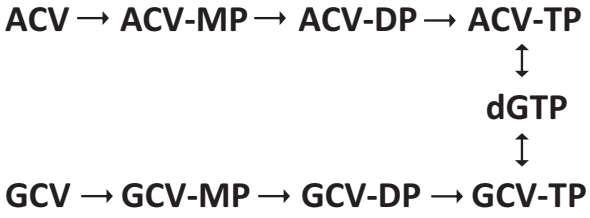

Fig. 1. Formules of (val)aciclovir, (val)ganciclovir and modes of action of acyclovir (ACV) and ganciclovir (GCV).

the triphosphate (ACV-TP) by a nucleoside diphosphate (NDP) kinase. ACV-TP then competes with the natural substrate dGTP for incorporation into the (viral) DNA by the (viral) DNA polymerase and, as ACV is missing the 3′-hydroxyl group necessary for further chain elongation, ACV-TP obligatorily acts as a chain terminator.

3. Bromovinyldeoxyuridine (Fig. 2)

The 5-substituted 2′-deoxuridines IDU and TFT were launched for clinical use in the topical treatment of herpetic eye infections (i.e. HSV keratitis) thanks to the pioneering efforts of H. Kaufman