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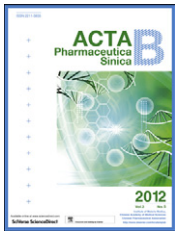

REVIEW

Milestones in the discovery of antiviral agents: nucleosides and nucleotides

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KEY WORDS

Valacyclovir;
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Cidofovir;
Adefovir;
Tenofovir;
Truvada®;
Phosphonoamidate

Abstract In this review article, a number of milestones in the antiviral research field on nucleosides and nucleotides are reviewed in which the author played a significant part, especially in the initial stages of their development. Highlighted are the amino acyl esters of acyclovir, particularly valacyclovir (VACV), brivudin (BVDU) and the valine ester of Cf1743 (FV-100), the 2′,3′-dideoxynucleosides (nucleoside reverse transcriptase inhibitors, NRTIs), the acyclic nucleoside phosphonates (*S*)-HPMPA, (*S*)-HPMPC (cidofovir) and alkoxyalkyl esters thereof (HDP-, ODE-CDV), adefovir and adefovir dipivoxil, tenofovir and tenofovir disoproxil fumarate (TDF), combinations containing TDF and emtricitabine, i.e., Truvada®, Atripla®, Complera®/Eviplera® and the Quad pill, and the phosphonoamidate derivatives GS-7340, GS-9131, GS-9191 and GS-9219.

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1. Introduction

The era of antiviral drug therapy started with idoxuridine (IDU) and trifluridine (TFT). IDU was first synthesized as a potential anticancer drug by Prusoff in 1959[1]; it was first shown in 1961 to possess activity against herpes simplex virus (HSV) and vaccinia virus by Herrmann[2], before it was launched in the clinic, for the topical treatment of herpetic keratitis by Kaufman[3]. Two years later, Kaufman and heidelbrger[4] also unleashed trifluridine (TFT) for the topical treatment of herpetic keratitis. As of today, IDU and TFT are still used in the topical treatment of herpetic eye infections.

Still in the 1960s, arabinosyladenine (ara-A), originally synthesized as a potential anticancer agent by Lee et al.[5] was first shown by Privat de Garilhe and de Rudder[6] to be active against HSV and vaccinia virus before it was further described as an antiviral agent by Schabel[7], before it became the first antiviral drug to be used systemically, i.e., by Whitley et al.[8] in 1976, in the therapy of varicella-zoster virus (VZV) infections. Ara-A is no longer used in the clinic, essentially for a number of reasons: it has low aqueous solubility, is rapidly deaminated to the inactive arabinosylhypoxanthine (ara-Hx), but primarily, because it was superseded from the 1980s by acyclovir.

Meanwhile, in the early 1970s ribavirin (virazole) had been described by Sidwell et al.[9] as a broad-spectrum antiviral agent. For *circa* 30 years, ribavirin was looking for a disease against which it could be useful, until it found its niche, together with pegylated interferon, in the treatment of chronic hepatitis C virus (HCV) infections. The combination of pegylated interferon-α with ribavirin has since the last 10 years been the standard of care (SOC) for the treatment of HCV infections, but is likely to be, first complemented and then replaced by direct-acting antiviral agents (DAAs).

Of crucial importance in the treatment of herpesvirus (i.e., HSV and VZV) infections was the discovery of acyclovir, the first truly specific antiviral agent, by Elion et al.[10] and Schaeffer et al[11]. Now, 35 years after it was originally described, acyclovir can still be considered as the "gold standard" for the treatment of HSV and VZV infections[12].

How the antiviral research field, that started with the nucleoside analogs IDU, TFT, ara-A, ribavirin and acyclovir, further evolved (and thrived) will be the subject of the present review. This review will focus specifically on nucleoside analogs such as amino acyl acyclovir esters, bromovinyldeoxyuridine and 2′,3′-dideoxynucleoside analogs, and nucleotide analogs (i.e., acyclic nucleoside phosphonates (ANPs)). Twenty-five years ago, the era of the ANPs started with the birth of (*S*)-HPMPA. It has now grown to a large family of marketed drugs, including cidofovir, adefovir and tenofovir, and various prodrugs and drug combinations derived thereof.

2. Antiviral agents

2.1. Valacyclovir (VACV)

Acyclovir suffers from some drawbacks in that it is relatively insoluble in aqueous medium and poorly absorbed after oral administration. To circumvent the first problem, amino acid (i.e., glycine, alanine) esters of acyclovir (Fig. 1) were synthesized[13]. An advantage of such amino acyl esters is that for topical use, i.e., for the treatment of herpetic keratitis, they can

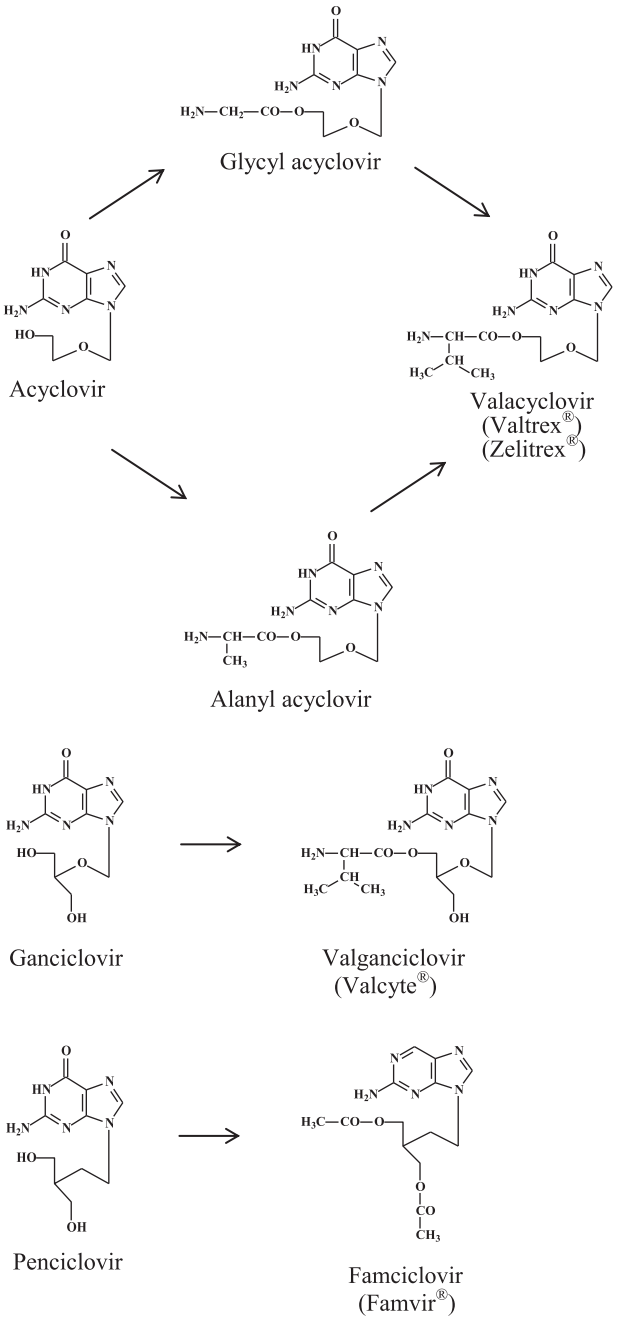

Figure 1 Prodrugs of acyclovir, ganciclovir and penciclovir.

be administered as eye drops[14], whereas acyclovir has to be applied as an eye ointment. A second advantage of such amino acyl esters is that for systemic use they could be injected intramuscularly or subcutaneously, in small volumes, whereas the parent compound, acyclovir, has to be administered intravenously in large volumes. However, from a practical viewpoint, parenteral injection of the amino acid esters of acyclovir has never been pursued.

Of the various amino acid esters of acyclovir that were subsequently studied, the valine ester, valacyclovir (Zelitrex®, Valtrex®) (Fig. 1) appeared to be the most suitable for increasing the oral bioavailability of acyclovir[15], and valacyclovir has now replaced acyclovir in the oral treatment of HSV and VZV infections. Likewise, to increase the oral bioavailability,