Immunomodulatory antivirals

Antiviral activity of nucleoside derivatives

Antiviral activity is the most prominent feature of several nucleoside and nucleotide derivatives. They are usually broad-spectrum compounds that inhibit replication of both DNA and RNA viruses, including retroviruses. Three dideoxynucleotides [3′-azido-2′,3′-dideoxythymidine (AZT; zidovudine), 2′,3′-dideoxyinosine (ddI; didanosine) and 2′,3′-dideoxycytidine (ddC; zalcitabine)] have been aproved for treatment of AIDS [Yarchoan, R. *et al. Lancet* (1986) i, 575–580; Ahluwalia, G. *et al. Biochem. Pharmacol.* (1987) 36, 3797–3800; Yarchoan, R. *et al. Lancet* (1988) 1, 76–81].

Holy, A. and coworkers at the Institute of Organic Chemistry and Biochemistry (Prague, Czech Republic) have developed a novel group of antivirals in which the sugar moiety in the nucleoside molecule was replaced by an acyclic hydroxylated chain and the phosphonomonoester linkage was altered to isopolar conformationally adaptable nucleotide derivatives. These compounds bearing an RO-CH_2-PO_3H_2 group are generally called acyclic nucleoside phosphonates (ANP).

Intracellular activation

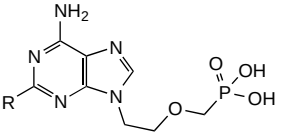
The antiviral activity of these compounds is acquired after transformation by intracellular kinases to the mono- and diphosphoryl derivatives. The phosphorylation does not depend on viral thymidine kinase and thus they are also effective against thymidine kinase-deficient viruses [Maudgal, P.C. and De Clercq, E. *Antiviral Res.* (1991) 16, 93–100]. It is assumed that the cytostatic activity of ANPs is caused mainly by suppression of cellular DNA synthesis mediated by inhibition of replicative DNA-polymerases.

The major disadvantages of these drugs are rather poor intracellular delivery, limited intestinal absorption and low oral bioavailability. However, these parameters have been greatly improved by esterification with lipophilic pivaloyloxymethyl (POM) or isopropyloxycarbonyloxymethyl (POC) groups.

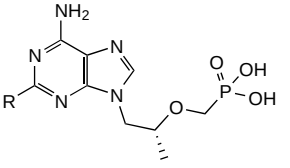
Broad antiviral activity

The antiviral activity of ANPs encompass herpes simplex virus-1 and -2, human herpes virus type 6, cytomegalovirus, varicella zoster virus, Epstein-Barr virus, human papilloma virus, Moloney sarcoma virus, hepatitis B virus, Friend leukemia virus, human immunodeficiency virus types 1 and 2, simian immunodeficiency virus and feline immunodeficiency virus. Several ANPs have shown therapeutic value:

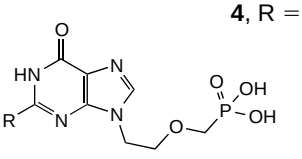
- The orally bioavailable and therapeutically more efficacious ester of the prototype compound 9-(2-phosphonomethoxyethyl)adenine (PMEA; adefovir; 1) – bis-POM-PMEA (adefovir dipivoxil; Prevenon™) – entered Phase II/III clinical development for treatment of HIV and Phase II clinical trials for hepatitis B virus.
- Outstanding effects against replication of retroviruses including HIV were observed with 9-(2-phosphonomethoxypropyl)adenine (PMPA; **3**), where it completely prevented development of AIDS in a simian model of the immunodeficiency disease [Tsai, C-C. *et al. Science* (1995) 270, 1197–1199]. Oral, intravenous and topical pharmaceutical formulations have been cleared for treatment of HIV.
- The 9-(2-phosphonomethoxyethyl)-2,6-diaminopurine (PMEDAP; **2**) and 9-(2-phosphonomethoxypropyl)-2,6-diaminopurine (PMPDAP; **4**) also display very high activity against retroviruses and DNA viruses [Balzarini, J. *et al. Biochem. Biophys. Res. Commun.* (1996) 219, 337–341].
- The cytosine analogue 1-(3-hydroxy-2-phosphonomethoxypropyl) cytosine (cidofivir, Vistide™) was approved for treatment of cytomegalovirus retinitis in AIDS patients [Lalezari, J.P. *et al. J. Infect. Dis.* (1995) 171, 788–796].
- The 9-(2-phosphonomethoxy-ethyl) guanine (PMEG; **5**), is highly effective against papilloma virus [Krieder, J.W. *et al. Antiviral Res.* (1990) 14, 51–58].



1, R = H
2, R = NH_2



3, R = H
4, R = NH_2



5

Immunomodulatory and pharmacological profile of ANPs

As well as exhibiting strong inhibitory effects upon proliferation of lymphocytes [Holy, A. *et al. Collect. Czech. Chem. Commun.* (1996) 61, 182–187], ANPs have been found to be potent activators of cytokine gene expression. Thus, PMEA stimulates production *in vivo* of interferon α/β (IFN-α/β) in murine mononuclear cells and increases natural killer cell cytotoxicity [Del Gobbo, V. *et al. Antiviral Res.* (1991) 16, 65–75]. Several of the most prominent compounds of the series, including **1**–**5**, are inducers of IFN-γ, tumour necrosis factor α (TNF-α) and interleukin 10 (IL-10) secretion, and they substantially enhance formation of nitric oxide (NO) by macrophages

 1359-6446/99/$ – see front matter PII: S1359-6446(98)01286-0

[Zidek, Z. *et al. Int. J. Immunopharmacol.* (1997) 19, 587–597]. Novel vistas for extension of therapeutic applications of ANPs, hitherto recognized only for antiviral properties, have recently been indicated by the discovery that PMEA inhibits pathogenetic processes playing a role in the development of rat adjuvant-induced arthritis – a model of human rheumatism [Zidek, Z. *et al. Eur. J. Pharmacol.* (1995) 286, 307–310]. Some ANPs have also been shown to suppress tumour growth [Rose, W.C. *et al. J. Natl. Cancer Inst.* (1990) 82, 510–512].

Benefit versus harm

Pharmacologists, toxicologists and clinicians should be aware of the immunomodulatory potential of these drugs, as sustained activation of the immune system may be beneficial or harmful depending upon the conditions. Thus, while IFN-γ plays a key role in host defense, it has been implicated in the pathogenesis of some diseases, such as septic shock and certain autoimmune diseases [Farrar, M.A. and Schreiber, R.D. *Annu. Rev. Immunol.* (1993) 11, 571–611; Boehm, U. *et al. Annu. Rev. Immunol.* (1997) 15, 749–795]. Uncontrolled production by macrophages of various proinflammatory cytokines, which are otherwise important in early defense mechanisms against invading pathogens, may mediate various diseases designated as a macrophage-activation syndrome. The production of NO by cytokine-activated macrophages and also many other cell types has proved to be a powerful means of nonspecific defense against several microorganisms, including viruses. It has been suggested that NO inhibits very early events in viral replication and thus enhances recovery of the host [Reis, C.S. and Komatsu, T.J. *Virology* (1998) 72, 4547–4551]. NO has significant (patho)physiological roles in the cardiovascular and nervous systems as well as the immune system. However, sustained over-production of NO may be followed by formation of toxic products such as peroxynitrite and nitrotyrosine leading to tissue and DNA damage, and thus representing a potential risk to a patient [Szabó, J. *Shock* (1996) 6, 79–88].

It would be important to investigate the immunobiological effects of other nucleoside-based antivirals, and to evaluate to what extent these properties are relevant to their antiviral efficacy. The data indicate that rapidly progressing development and clinical use of such drugs should be tightly associated with careful monitoring of their immunobiological potential. Hopefully, this may provide a better understanding of mechanisms of their action and lead to the development of more-active and specific compounds. This will enhance clinical safety as well as extend their therapeutic modalities.

Zdenek Zídek
Institute of Pharmacology
Prague, Czech Republic
fax: +420 2 475 2109
e-mail: zidekz@biomed.cas.cz