2. ANTIMICROBIAL ACTIVITY

2a. Routine susceptibility

Adefovir has activity against hepadnaviruses and some herpesviruses and retroviruses but no activity against other RNA or DNA viruses, including adenoviruses, poxviruses, and papillomaviruses (De Clercq, 2003; De Clercq, 2007; Table 255.1 and Table 255.2). Adefovir has been used predominantly in the treatment of chronic HBV infections, although it is also useful for treating chronic HBV in the pre- and postliver transplant setting (discussed later in this chapter). It was previously investigated briefly as a treatment for HIV infection, but because the high doses used in the HIV phase III trials (120–500 mg) resulted in dose-limiting nephrotoxicity (discussed later in this chapter), it was not approved for this indication.

HEPADNAVIRUSES

Early *in vitro* studies showed that adefovir inhibited the replication of human HBV and duck HBV (see Table 255.1). Adefovir therapy markedly reduced viral DNA load in woodchuck hepatitis virus (Cullen *et al.*, 2001) and in the liver and serum of transgenic mice expressing HBV (Julander *et al.*, 2002).

Adefovir and its prodrug, adefovir dipivoxil, are active *in vitro* against both wild-type HBV and recombinant HBV variants containing lamivudine resistance-associated mutations (rtL180M, rtM204I, rtM204V, rtL180M + rtM204V, rtL180M + rtM204V + rtV173L) in the HBV DNA polymerase gene (Schiff *et al.*, 2003; Westland *et al.*, 2005). Adefovir is also active *in vitro* against HBV variants with DNA polymerase mutations, including the rtT128N and W153Q mutations (associated with resistance to HBV immunoglobulin). The *in vitro* concentration of adefovir required to inhibit by 50% (EC_{50}) replication of wild-type HBV is 0.2–2.5 μM in human hepatic cell lines. These EC_{50} values are significantly lower than the EC_{50} concentrations required to inhibit either human cell growth or DNA synthesis (50% cytotoxicity concentration [CC_{50}]) (Dando and Plosker, 2003). CC_{50} and selectivity (CC_{50}:EC_{50}) ratios range from 20 to 150 μM/l and from 10 to 537 μM/l.

In vitro studies investigating adefovir in two-drug combinations with penciclovir or lamivudine show the antiviral effects to be additive or synergistic against duck HBV (Colledge *et al.*, 2000). Adefovir also has additive antiviral activity when combined with lamivudine, entecavir, or telbivudine against cell lines expressing high levels of wild-type HBV (HepG2 49-29) (Dando and Plosker, 2003).

Table 255.2. Inhibition of viral and cellular DNA polymerases by adefovir.

DNA polymerase	Inhibition constant (K_i)
Herpes simplex virus 1 DNA polymerase	0.11 μM
HIV-1 reverse transcriptase	
DNA template	0.98 μM
RNA template	0.012 μM
Human DNA polymerase alpha	1.18 μM
Human DNA polymerase beta	70.4 μM
Human DNA polymerase gamma	0.97 μM
Human DNA polymerase delta	0.41 μM
Human DNA polymerase epsilon	0.67 μM
Hepatitis B virus DNA polymerase	0.1 μM/l (adefovir diphosphate)

Source: Adapted with permission from Naesens and Andrei (1997).

OTHER VIRUSES

Early *in vitro* studies show that adefovir inhibits varicella-zoster virus (VZV), human cytomegalovirus (HCMV), and Epstein-Barr virus (EBV) (see Table 255.1). Adefovir is also active against some retroviruses: simian immunodeficiency virus (SIV) and feline immunodeficiency virus (FIV), visnamaedi virus of sheep, and murine leukemia and sarcoma viruses (Naesens and Andrei, 1997).

Subsequent studies showed that adefovir had moderate antiviral activity against EBV (ADHOC International Steering Committee, 2002; Rossi *et al.*, 2002; Gershburg and Pagano, 2005), HCMV (Balzarini *et al.*, 1991), and cytomegalovirus (CMV) (Katlama, 1996; Hoffman and Skiest, 2000). Adefovir is not effective against the hepatitis delta virus (Wedemeyer *et al.*, 2011)

Adefovir has been reported to have activity against HIV (Mulato and Cherrington, 1997; Naesens and Andrei, 1997; Palmer *et al.*, 2001; ADHOC International Steering Committee, 2002). However, a clinical trial showed no virologic or immunologic benefit when adefovir was added to background antiretroviral therapy in advanced HIV disease (Fisher *et al.*, 2001). Of greater importance, the high doses of adefovir used in phase III trials for treatment of HIV infection (120–500 mg) resulted in dose-limiting nephrotoxicity (Barditch-Crovo *et al.*, 1997; Deeks *et al.*, 1997; Kahn *et al.*, 1999; ADHOC International Steering Committee, 2002). The modest reductions in viral load coupled with significant risks of nephrotoxicity at doses needed to treat HIV virus caused adefovir to be abandon for this indication (De Clercq, 2003).

Early *in vitro* studies report that adefovir was active against herpes simplex virus 1 (HSV-1), thymidine kinase (TK) HSV-1 (TK-deficient, aciclovir-resistant), HSV-2, and human herpesvirus (HHV) (see Table 255.1). The *in vitro* combinations of hydroxyurea and adefovir are synergistically active against HSV-1 and HSV-2 (Neyts and De Clercq, 1999). Adefovir is also shown to have potent *in vitro* activity against human HSV-6 (Bronson *et al.*, 1989) and against murine gamma herpesvirus 68 (Neyts and De Clercq, 1998). Significant inhibitory activity has also been reported against Kaposi sarcoma–associated herpesvirus (HHV 8) (Neyts and De Clercq, 1997).

Adefovir dipivoxil (not adefovir) has been reported to have activity against vaccinia virus and cowpox virus in tissue culture cells (Keith *et al.*, 2003). The *in vivo* utility of this finding has not been established.