Review Article

Drug Therapy

ALASTAIR J.J. WOOD, M.D., *Editor*

ANTIVIRAL DRUGS

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ELEVEN drugs approved by the Food and Drug Administration for the treatment of viral infections (other than those caused by human immunodeficiency virus type 1 [HIV-1] or those complicating such infection) will be reviewed in this article. They are seven nucleoside analogues, two closely related 10-carbon-ring amines, one pyrophosphate analogue, and a recombinant protein produced in bacteria (Fig. 1). The characteristics of these antiviral drugs are given in Table 1, management of their adverse effects is outlined in Table 2, and specific recommendations for their use are provided in Table 3.

APPROVED DRUGS

Acyclovir

Acyclovir is an analogue of 2′-deoxyguanosine that exerts its antiviral effect after being metabolized to acyclovir triphosphate (Fig. 2). The initial step in this process, the formation of acyclovir monophosphate, is catalyzed by a thymidine kinase induced in cells infected with herpes simplex virus[1,2] or varicella–zoster virus[3] or by a phosphotransferase produced by cytomegalovirus.[4] Cellular enzymes next add phosphates to form acyclovir diphosphate and acyclovir triphosphate. Acyclovir triphosphate inhibits the synthesis of viral DNA by competing with 2′-deoxyguanosine triphosphate as a substrate for viral DNA polymerase.[1,2] Once acyclovir (rather than 2′-deoxyguanosine) is inserted into the replicating viral DNA, synthesis stops (Fig. 2). The incorporation of acyclovir monophosphate into viral DNA is irreversible, because the polymerase-associated 3′,5′-exonuclease cannot excise it.[5] In this process, the viral DNA polymerase is also inactivated.[6]

Acyclovir triphosphate is 30 to 50 times as potent an inhibitor of herpes simplex type 1 DNA polymerase as of human cellular alpha-DNA polymerase.[6] The meager production of acyclovir triphosphate in uninfected cells and its specificity for viral DNA polymerase result in minimal cellular toxic effects. In addition, more than 80 percent of the acyclovir that reaches the circulation is excreted unchanged in the urine.[7]

The median 50 percent inhibitory concentration of acyclovir against herpes simplex virus type 1 is 0.1 μM,[8] and it is 0.4 μM against herpes simplex virus type 2,[8] 2.6 μM against varicella–zoster virus,[9] and 47.1 μM against cytomegalovirus.[10] Despite poor oral bioavailability, plasma acyclovir concentrations greatly exceeding the 50 percent inhibitory concentration against herpes simplex virus types 1 and 2 are attained in adults after the administration of 200 mg of acyclovir.[8] In contrast, 800 mg is necessary to provide plasma concentrations above the median 50 percent inhibitory concentration for varicella–zoster virus.[8] Because acyclovir has a relatively short half-life in plasma[7] (Table 1), 800 mg must be given every four to six hours to patients infected with varicella–zoster virus (Table 3). Acyclovir has proved effective for the treatment of infections caused by herpes simplex virus types 1 and 2[11,12] and varicella–zoster virus[13,14] and for the suppression of some forms of cytomegalovirus disease.[15]

Valacyclovir

Valacyclovir, the L-valyl ester of acyclovir, is available only as an oral formulation. After ingestion, the drug is rapidly converted to acyclovir by the enzyme valacyclovir hydrolase in the gastrointestinal tract and liver.[16] Its oral bioavailability is three to five times that of acyclovir (Table 1).[16] Valacyclovir has proved effective in the treatment of infections caused by herpes simplex virus[17] and varicella–zoster virus[18] and as prophylaxis against cytomegalovirus disease.[19]

Ganciclovir

Ganciclovir, which was recently reviewed in the *Journal*,[20] differs from acyclovir by the addition of a hydroxymethyl group at the 3′ position of the acyclic side chain (Fig. 1). Its metabolism and mechanism of action are similar to those of acyclovir, except that it has a 3′ carbon with a hydroxyl group that can permit primer–template extension (Fig. 2) and so is not an absolute DNA-chain terminator.[21]

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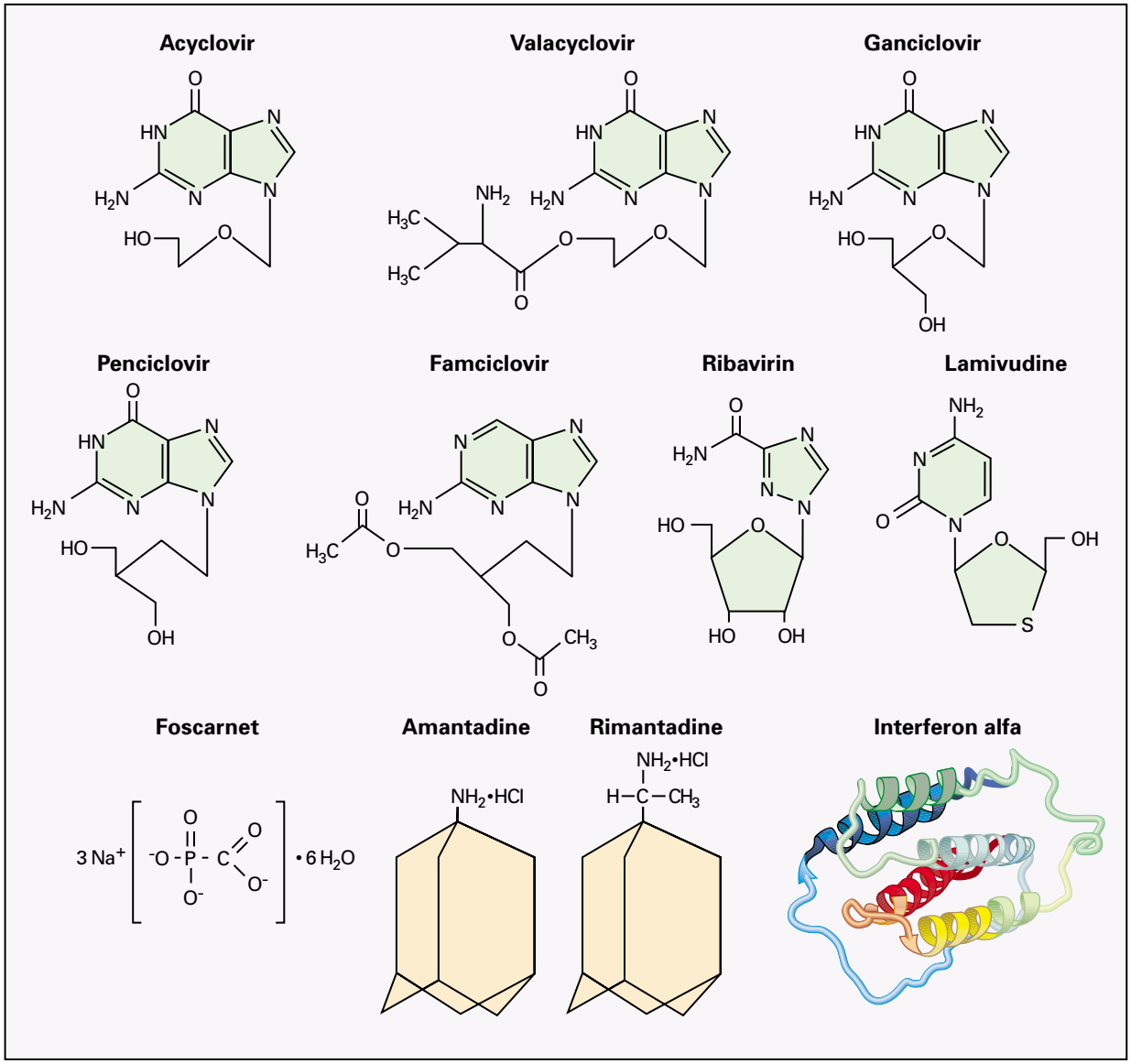

Figure 1. Structures of 11 Antiviral Drugs.

Six of the 11 drugs resemble the natural nucleoside 2′-deoxyguanosine, and 2 others are analogues of aminoadamantane. Interferon alfa is shown as a computer-generated three-dimensional model in monomeric form. It is much larger than the others (molecular weight, 19,271).

Ganciclovir is converted to ganciclovir monophosphate by a viral-encoded phosphotransferase produced in cells infected with cytomegalovirus.[22,23] It is a better substrate than acyclovir for this phosphotransferase, and the intracellular half-life of ganciclovir triphosphate is at least 12 hours, as compared with 1 to 2 hours for acyclovir (Table 1).[4] This difference is the reason why ganciclovir is superior to acyclovir for the treatment of cytomegalovirus disease. The peak plasma concentration after intravenous administration of usual doses greatly exceeds the 3 μM needed to inhibit the majority of strains of cytomegalovirus.[24,25] Intravenous ganciclovir is effective for the suppression and treatment of cytomegalovirus disease.[24,26,27] Oral ganciclovir has also proved useful for the suppression of cytomegalovirus disease,[28] but its value is limited by its low bioavailability (8 to 9 percent).[29]

Penciclovir

Penciclovir is structurally similar to ganciclovir, differing only by the substitution of a methylene

TABLE 1. CHARACTERISTICS OF 11 ANTIVIRAL DRUGS.*

ANTIVIRAL DRUG	MECHANISM OF ACTION	VIRUSES AFFECTED		PHARMACOLOGIC PROPERTIES
		PROVED†	POSSIBLE‡	
Acyclovir	Metabolized to acyclovir triphosphate, which inhibits viral DNA polymerase	Herpes simplex, varicella–zoster, cytomegalovirus	Epstein–Barr, herpes B (herpes simiae)	Oral bioavailability, 10–20%; plasma half-life, 2–3 hr; intracellular half-life of acyclovir triphosphate, 1–2 hr§
Valacyclovir	Same as acyclovir	Herpes simplex, varicella–zoster, cytomegalovirus		Oral bioavailability, 54%; plasma half-life, 2–3 hr; intracellular half-life, 1–2 hr§
Ganciclovir	Metabolized to ganciclovir triphosphate, which inhibits viral DNA polymerase	Cytomegalovirus	Herpes simplex, varicella–zoster, Epstein–Barr, human herpesvirus 8, herpes B (herpes simiae)	Oral bioavailability, 8–9%; plasma half-life, 2.5 hr; intracellular half-life of ganciclovir triphosphate, 12 hr§
Penciclovir	Metabolized to penciclovir triphosphate, which inhibits viral DNA polymerase	Herpes simplex		Only available topically, with no appreciable systemic absorption; intravenous formulation under development
Famciclovir	Same as penciclovir	Herpes simplex, varicella–zoster	Hepatitis B	Oral bioavailability, 77%; plasma half-life, 2 hr; intracellular half-life of penciclovir triphosphate, 7–20 hr§
Foscarnet	Inhibition of viral DNA polymerase and reverse transcriptase at the pyrophosphate-binding site	Cytomegalovirus, acyclovir-resistant herpes simplex, acyclovir-resistant varicella–zoster	Human herpesvirus 8, human immunodeficiency virus type 1	Oral bioavailability, 0%; plasma half-life, 6 hr; triphasic elimination due to deposition in bone matrix
Ribavirin	Interference with viral messenger RNA	Lassa fever, hantavirus (hemorrhagic fever renal syndrome), hepatitis C (in chronic cases in combination with interferon alfa)	Respiratory syncytial virus, parainfluenza, influenza A and B, measles, hantavirus (pulmonary syndrome)	Oral bioavailability, 32%; plasma half-life, 30–60 hr; some absorption of aerosolized formulation
Lamivudine	Inhibition of viral DNA polymerase and reverse transcriptase	Hepatitis B (chronic cases), human immunodeficiency virus type 1		Oral bioavailability, 86%; plasma half-life, 5–7 hr
Amantadine	Blockage of the M2 protein ion channel and its ability to modulate intracellular pH	Influenza A		Oral bioavailability, >90%; plasma half-life, 10–31 hr in young adults; peak concentrations higher and plasma half-life longer in patients ≥60 years old
Rimantadine	Blockage of the M2 protein ion channel and its ability to modulate intracellular pH	Influenza A		Oral bioavailability, >90%; plasma half-life, 25–36 hr; 75% of drug is metabolized in liver
Interferon alfa	Induction of cellular enzymes that interfere with viral protein synthesis	Hepatitis B and C, human herpesvirus 8, papillomavirus	Hepatitis D	Oral bioavailability, 0%; plasma half-life, 2–3 hr

*This list excludes drugs used exclusively for human immunodeficiency virus type 1 infection.

†Safety and efficacy have been documented in controlled clinical trials.

‡Efficacy is supported by uncontrolled clinical data or results of in vitro susceptibility studies.

§Intracellular half-lives are based on in vitro data.

bridge for the ether oxygen in the acyclic ribose part of the molecule (Fig. 1). Its metabolism and mechanism of action are similar to those of acyclovir, except that it is not an obligate DNA-chain terminator[30] (Fig. 2). The in vitro inhibitory effects of penciclovir on herpes simplex virus types 1 and 2 and varicella–zoster virus are similar to those of acyclovir.[31]

The oral bioavailability of penciclovir is poor. At present, it has been approved only as a topical formulation for the treatment of herpes labialis. An intravenous preparation is being studied as a treatment for mucocutaneous herpes in immunocompromised patients.

Famciclovir

Famciclovir is the diacetyl-6-deoxy analogue of penciclovir (Fig. 1). It is well absorbed after oral administration and is rapidly metabolized to penciclovir by deacetylation in the gastrointestinal tract, blood, and liver, after which it is oxidized by the liver

TABLE 2. ADVERSE EFFECTS OF ANTIVIRAL DRUGS AND THEIR MANAGEMENT.*

ANTIVIRAL DRUG	ADVERSE EFFECT	FREQUENCY	CAUSE	MANAGEMENT
Acyclovir	Reversible nephropathy	Uncommon	Crystallization of drug in renal tubules, almost exclusively after intravenous administration	Give 1 liter of fluid per gram of acyclovir; infuse each dose at a rate of 6 mg/ml or less over a 1-hr period; reduce dose in patients with renal insufficiency according to creatinine clearance.
	Gastrointestinal disturbances	Uncommon	Direct effect	Reduce dose if necessary.
	Irritation at infusion site, phlebitis	Uncommon	High alkalinity of acyclovir in solution (pH, 11)	Ensure that intravenous device is intact, with no extravasation.
	Headache	Uncommon	Direct effect on central nervous system or effect of metabolite (carboxymethoxymethyl guanine)	Reduce dose.
	Rash	Rare	Idiosyncratic	Discontinue drug for moderate-to-severe rashes.
	Encephalopathy	Rare	Precipitated by renal failure or by other drugs with adverse central nervous system effects	Discontinue drug.
Valacyclovir	Same as for acyclovir	Same as for acyclovir	Same as for acyclovir	Same as for acyclovir.
	Thrombotic microangiopathy	Rare	Unknown; appears limited to immunosuppressed patients receiving multiple drugs	Discontinue drug.
Ganciclovir	Bone marrow suppression, especially granulocytopenia	Common	Direct effect	Reduce dose; reduce or discontinue other marrow-suppressive drugs; administer granulocyte growth factors.
	Renal insufficiency	Uncommon	Probably crystallization of drug in renal tubules	Ensure adequate hydration; reduce dose in patients with renal insufficiency according to creatinine clearance.
	Fever, headache	Uncommon	Probably a direct effect	Reduce dose if necessary.
	Irritation at infusion site, phlebitis	Uncommon	Alkalinity of drug	Ensure that intravenous device is intact, with no extravasation.
	Rash	Rare	Idiosyncratic	Discontinue drug for moderate-to-severe rashes.
	Encephalopathy	Rare	Probably direct toxic effect augmented by other drugs with adverse central nervous system effects	Discontinue drug.
Penciclovir	None†			
Famciclovir	Headache, nausea, diarrhea	Uncommon	Probably direct toxic effects	Reduce dose if necessary.
	Interactions with drugs inhibiting or requiring hepatic oxidation	Theoretical	Oxidation of drug in liver	Dose reduction may be necessary in patients with hepatic insufficiency; mutagenesis and carcinogenicity have been reported in laboratory animals.
Foscarnet	Renal insufficiency	Common	Direct damage to renal tubules	Hydrate with up to 2 liters of isotonic saline before administration; monitor renal function during therapy; reduce dose in patients with renal failure according to manufacturer's instructions.
	Electrolyte imbalance, especially hypocalcemia	Common	Chelation of divalent metal cations	Measure serum electrolytes at least twice weekly during first 2 weeks of therapy, and provide oral or intravenous replacement as needed.
	Nausea, vomiting	Common	Direct effect or due to electrolyte imbalance	Dose reduction is usually not necessary.
	Anemia	Uncommon	Direct effect on bone marrow	Dose reduction is usually not necessary.
	Penile ulcers	Uncommon	Contact dermatitis due to local accumulation of foscarnet	Hydrate before administration and maintain adequate hygiene.
	Seizures	Rare	Direct effect or due to electrolyte imbalance	Discontinue drug.

at position 6 of the purine ring.[32] The intracellular half-life of the active drug, penciclovir triphosphate, is very long, suggesting the potential for once-daily dosing. Famciclovir is effective against genital herpes[33] and herpes zoster infections.[34]

Foscarnet

Foscarnet (trisodium phosphonoformate) is an organic analogue of inorganic pyrophosphate (Fig. 1). It forms complexes with viral DNA polymerase at its pyrophosphate-binding site, preventing cleavage of pyrophosphate from nucleoside triphosphates and thus blocking further primer–template extension (Fig. 2).[35] Foscarnet must be given intravenously, because a tolerable oral formulation has not been developed. It is not metabolized to any appreciable degree and is eliminated by glomerular filtration and tubular secretion. Clinical studies have proved foscarnet equivalent to ganciclovir for the treatment of cytomegalovirus disease[36] and superior to vidarabine for the treatment of infections caused by herpes simplex viruses that are resistant to acyclovir.[37]

TABLE 2. CONTINUED.

ANTIVIRAL DRUG	ADVERSE EFFECT	FREQUENCY	CAUSE	MANAGEMENT
Ribavirin‡	Anemia	Common	Hemolysis and possibly bone marrow suppression	Reduce dose.
	Skin, eye, and upper airway irritation§	Uncommon	Contact irritant	Avoid direct contact if possible.
	Bronchospasm	Uncommon	Direct irritant to mucosal tissues	Discontinue aerosolized form of the drug.
Lamivudine	Lactic acidosis and severe hepatomegaly with steatosis	Rare	Possible interference with mitochondrial function	Discontinue drug.
Amantadine	Nausea and anorexia	Common	Possible direct effect	Effects may resolve during therapy; reduce dose if necessary; because of its high (>90%) oral bioavailability and dependence on renal elimination, dose must be reduced by 50% in patients ≥65 years old; reduce dose in patients with renal insufficiency according to manufacturer's instructions.
	Central nervous system dysfunction	Uncommon	Dopaminergic effect on central nervous system	
	Death from overdose	Rare	Dopaminergic activity on cardiovascular system	
Rimantadine	Nausea and anorexia	Uncommon	Possible direct effect	Effects may resolve during therapy; reduce dose if necessary.
	Central nervous system dysfunction	Less frequent than with amantadine	Dopaminergic effect on central nervous system	Reduce dose by 50% in patients ≥65 years old, and patients with renal or hepatic failure.
Interferon alfa	Influenza-like symptoms	Common	Intrinsic pyrogenic effect or release of proinflammatory cytokines	For all adverse effects, reduce or withhold dose temporarily; discontinue if severity warrants.
	Gastrointestinal disturbances	Common		
	Central nervous system dysfunction, including depression	Common	Effect of immune dysregulation on psychoneuroendocrine function	
	Bone marrow suppression	Common	Antiproliferative effect	
	Autoimmune phenomena	Uncommon	Immune dysregulation	

*The list does not include drugs used exclusively to treat human immunodeficiency virus type 1 infection.

†No adverse effects were reported in a controlled trial of a 1 percent penciclovir cream.

‡Ribavirin is teratogenic in laboratory animals and thus may pose a threat to care givers exposed to the aerosolized form.

§This effect has been reported in health care workers as well as in patients exposed to the aerosolized form of the drug.

Ribavirin

Ribavirin is a guanosine analogue that has an incomplete purine ring rather than an acyclic ribose moiety (Fig. 1). After intracellular phosphorylation, ribavirin triphosphate interferes with early events in viral transcription, such as the capping and elongation of messenger RNA, and inhibits ribonucleoprotein synthesis.[38,39] It has a broad spectrum of activity in vitro against RNA viruses (Table 1). The concentration of the major metabolite — 1,2,4-triazole-3-carboxamide — is higher in the urine after oral administration than after intravenous administration, implying that the drug is degraded in the gastrointestinal tract and liver.[40] Aerosolized ribavirin is absorbed systemically, as indicated by the presence of measurable concentrations in the plasma.[41] Clinical efficacy has been demonstrated for the treatment of infections caused by hemorrhagic fever viruses (with oral and intravenous formulations of ribavirin)[42,43] and hepatitis C (with oral ribavirin in combination with interferon).[44]

Lamivudine

Lamivudine is a pyrimidine nucleoside originally developed as an antiretroviral drug (Fig. 1). It is a cytidine analogue that is metabolized intracellularly to lamivudine triphosphate, which inhibits hepatitis B DNA polymerase as well as HIV reverse transcriptase. Lamivudine is effective as monotherapy for the treatment of chronic hepatitis B and in combination with other antiretroviral drugs for the treatment of HIV-1 infection. Lamivudine has high oral bioavailability and a relatively long plasma half-life (five to seven hours), which make once-daily dosing feasible for patients with chronic hepatitis B.

Amantadine and Rimantadine

Amantadine hydrochloride is an amine with a unique 10-carbon ring; rimantadine hydrochloride is a homologue created by the insertion of a methylated carbon bridge between the amino group and the 10-carbon ring (Fig. 1). Both drugs appear to inhibit the replication of influenza A viruses by blocking the viral M2 protein ion channel, thereby reducing the effect of this viral protein on viral uncoating and pH regulation in infected cells.[45]

Amantadine has high oral bioavailability and many side effects, especially among patients 60 years old or older, in whom peak plasma concentrations are approximately three times as high as in younger adults given the same dose and the plasma half-life is about 12 hours longer.[46] Amantadine is eliminated by glomerular filtration and tubular secretion of the

TABLE 3. RECOMMENDATIONS FOR ANTIVIRAL THERAPY.*

DISEASE	TREATMENT OF CHOICE	ALTERNATIVE TREATMENT	PROPHYLACTIC OR SUPPRESSIVE TREATMENT	COMMENTS
Genital herpes, initial episode	Acyclovir, 200 mg orally 5 times daily or 400 mg 3 times daily for 10 days Valacyclovir, 1 g orally twice daily for 10 days Famciclovir, 250 mg orally 3 times daily for 5–10 days†	Acyclovir, 5 mg/kg intravenously every 8 hr for 5 days (severe cases only)		Effect of antiviral therapy on transmission is not known.
Genital herpes, recurrent episode	Acyclovir, 200 mg orally 5 times daily or 400 mg 3 times daily for 5 days Valacyclovir, 500 mg orally twice daily for 5 days Famciclovir, 125 mg orally twice daily for 5 days		Acyclovir, 200–400 mg orally 2–3 times daily for 1 yr or longer, if necessary Valacyclovir, 500–1000 mg orally once daily Famciclovir, 125–250 mg orally twice daily	Suppression is usually preferable to episodic treatment; daily dose should be titrated to the lowest amount required to prevent recurrences; efficacy and safety of suppression with valacyclovir and famciclovir for more than 1 yr are not known.
Herpes labialis in an otherwise healthy person	Penciclovir, 1% cream applied to skin or lips every 2 hr during waking hours for 4 days	Acyclovir, 200 mg orally 5 times daily for 5 days†	Acyclovir, 200 mg orally 5 times daily just before and during exposure to the sun†	Best results are obtained from early patient-initiated therapy; prophylaxis is effective for sun-induced episodes.
Mucocutaneous herpes in an immunocompromised patient	Acyclovir, 5 mg/kg intravenously every 8 hr for 7 days‡	Acyclovir, 400 mg orally 5 times daily for 10 days† Valacyclovir, 1 g orally 3 times daily for 7 days† Famciclovir, 500 mg orally twice daily for 7 days†	Acyclovir, 400 mg orally 3 times daily for 2–3 mo† Valacyclovir, 1 g orally 3 times daily for 2–3 mo† Famciclovir, 500 mg orally twice daily for 2–3 mo†	Intravenous penciclovir appears to be equivalent to intravenous acyclovir.
Mucocutaneous herpes due to acyclovir-resistant virus	Foscarnet, 40 mg/kg intravenously 2–3 times daily for 7–21 days			Cidofovir gel is being evaluated for acyclovir-resistant herpes.
Herpes encephalitis	Acyclovir, 10–15 mg/kg intravenously every 8 hr for 14–21 days‡			Treat before semicoma or coma develops; morbidity and mortality are high despite treatment.
Neonatal herpes	Acyclovir, 10–15 mg/kg intravenously every 8 hr for 14 days†			Morbidity and mortality are high despite treatment for disseminated disease; suppression after initial therapy is being evaluated.
Chickenpox in an immunocompetent patient	Acyclovir, 20 mg/kg (maximum, 800 mg) orally 4 times daily for 5 days			Adolescents, adults, and patients with secondary cases in families are most likely to benefit from treatment.
Chickenpox in an immunocompromised patient	Acyclovir, 10 mg/kg intravenously every 8 hr for 7–10 days†‡		Varicella–zoster immune globulin, 1 vial/10 kg intramuscularly (maximum, 5 vials)	Treat as soon as possible to prevent visceral dissemination; immune globulin must be given within 96 hr after exposure.
Herpes zoster in an immunocompetent patient	Valacyclovir, 1 g orally 3 times daily for 7 days Famciclovir, 500 mg orally every 8 hr for 7 days	Acyclovir, 800 mg orally 5 times daily for 7 days		Patients ≥50 years or those with ophthalmic zoster are most likely to benefit from treatment.
Herpes zoster in an immunocompromised patient	Acyclovir, 10 mg/kg intravenously every 8 hr for 7 days‡	Foscarnet (for acyclovir-resistant virus), 60 mg/kg intravenously 2–3 times daily for 7–14 days†	Acyclovir, 400–800 mg orally 4 times daily for up to 3 mo after transplantation†	Treatment can be started as long as new lesions are still forming.

intact drug,[47] and hence the altered pharmacokinetics in older adults are most likely due to declining renal function. Rimantadine is also absorbed well; 75 percent of a dose is metabolized in the liver, mainly by hydroxylation.[48] Older adults require a reduction in the dose, presumably because of an age-related decline in hepatic function. Both drugs are effective for the prevention and treatment of influenza A infections.[49,50]

Interferon Alfa

Natural interferons are glycoproteins with antiviral activity that is postulated to be due to the induction of cellular enzymes that interfere with the synthesis of viral proteins.[51] Commercial preparations of interferon alfa are slightly smaller than the natural proteins (molecular weight, approximately 19,000) and are made in bacteria by recombinant-DNA techniques (Fig. 1). Interferons are not orally bioavailable and need to be

TABLE 3. CONTINUED.

DISEASE	TREATMENT OF CHOICE	ALTERNATIVE TREATMENT	PROPHYLACTIC OR SUPPRESSIVE TREATMENT	COMMENTS
Cytomegalovirus disease in transplant recipients	Ganciclovir, 5 mg/kg intravenously twice daily for 14–21 days†	Foscarnet, 60 mg/kg intravenously every 8 hr for 14–21 days†	Acyclovir, 800 mg orally 4 times daily for 3 mo (in renal-transplant recipients)† Ganciclovir, 1 g orally 3 times daily with meals for 2–3 mo (in liver-transplant recipients) Acyclovir, 10 mg/kg intravenously every 8 hr for 1 mo, followed by 800 mg orally 4 times daily for at least 3 mo (in bone marrow–transplant recipients)†‡ Ganciclovir, 5–6 mg/kg intravenously 5–7 days/wk for 3 mo (in recipients of bone marrow, heart, or liver transplants)	Oral ganciclovir is probably best in patients undergoing heart and lung transplantation, but definitive data are not available. Valacyclovir is effective as prophylaxis in renal-transplant recipients. Intravenous ganciclovir should not be started until after engraftment in recipients of bone marrow transplants; recipients of heart transplants are usually given 5 mg/kg every 12 hr for the first 2 wk after transplantation; dosage may be reduced to 5 days/wk for outpatients.
Influenza A	Rimantadine, 200 mg orally daily for 5–7 days in adults; 5 mg/kg/day (maximum, 150 mg) for 5–7 days in children <10 yr§	Amantadine, 100 mg orally twice daily for 5 days in adults; 2.2 mg/kg (maximum, 75 mg) twice daily for 5 days in children <9 yr	Rimantadine or amantadine, same dose as for treatment for 10 days–6 wk after exposure during influenza season	Reduce dose in patients ≥65 yr; treatment has been associated with transmission of drug-resistant virus to family members.
Respiratory syncytial virus, severe pneumonitis	Ribavirin, 20 mg/ml of water (6 g of ribavirin in 300 ml of sterile water), delivered by a small-particle aerosol 18 hr/day for 3–7 days		Respiratory syncytial virus immune globulin, 750 mg/kg intravenously, or monoclonal antibody (palivizumab), 15 mg/kg intramuscularly, monthly during respiratory virus season in infants with prematurity, bronchopulmonary dysplasia, or both	Ribavirin therapy is not practical except for hospitalized patients, and efficacy has been questioned; aerosol can be delivered by respirator, mask, or tent.
Chronic hepatitis B	Interferon alfa, 5 million units daily or 10 million units 3 times weekly subcutaneously or intramuscularly for 16–24 wk			Relapses are common after interferon alfa is discontinued.
	Lamivudine, 100 mg orally once daily for up to 1 yr			This dosage of lamivudine used as monotherapy could lead to rapid emergence of resistant strains of human immunodeficiency virus in patients infected with both viruses.
Chronic hepatitis C	Interferon alfa, 3 million units subcutaneously or intramuscularly 3 times weekly, and ribavirin, 500–600 mg orally twice daily, for 24 wk			Combination of interferon alfa and ribavirin produced a significantly higher rate of sustained virologic responses than interferon alfa alone.

*In patients with renal failure, the dose may need to be reduced according to the manufacturer's instructions.

†The drug is not approved by the Food and Drug Administration for this indication.

‡The dose for children under 12 years of age is calculated according to body-surface area and should be 250 mg per square meter instead of 5 mg per kilogram or 500 mg per square meter instead of 10 mg per kilogram.

§The drug is not approved by the Food and Drug Administration for this indication in children.

given by intramuscular or subcutaneous injection. Reliable data on the inhibition of viral replication in vitro are not available, most likely because interferons exert their antiviral action by inhibiting viral RNA transcription and translation and by augmenting cellular immune function. Interferon alfa has proved effective for the treatment of diseases caused by papillomaviruses,[52] human herpesvirus 8 (Kaposi's sarcoma),[53] hepatitis B virus,[54] and hepatitis C virus.[44,55,56]

ADVERSE EFFECTS OF ANTIVIRAL DRUGS

Because viruses are obligate intracellular pathogens dependent on host-cell functions, skeptics once believed that selective inhibitors of viral replication could not be found. This belief was reinforced by failures with early antiviral drugs, such as systemic idoxuridine and cytarabine, and relatively recently with fialuridine.[57] Fortunately, drugs that have a greater effect on viral replication than on host-cell function have now

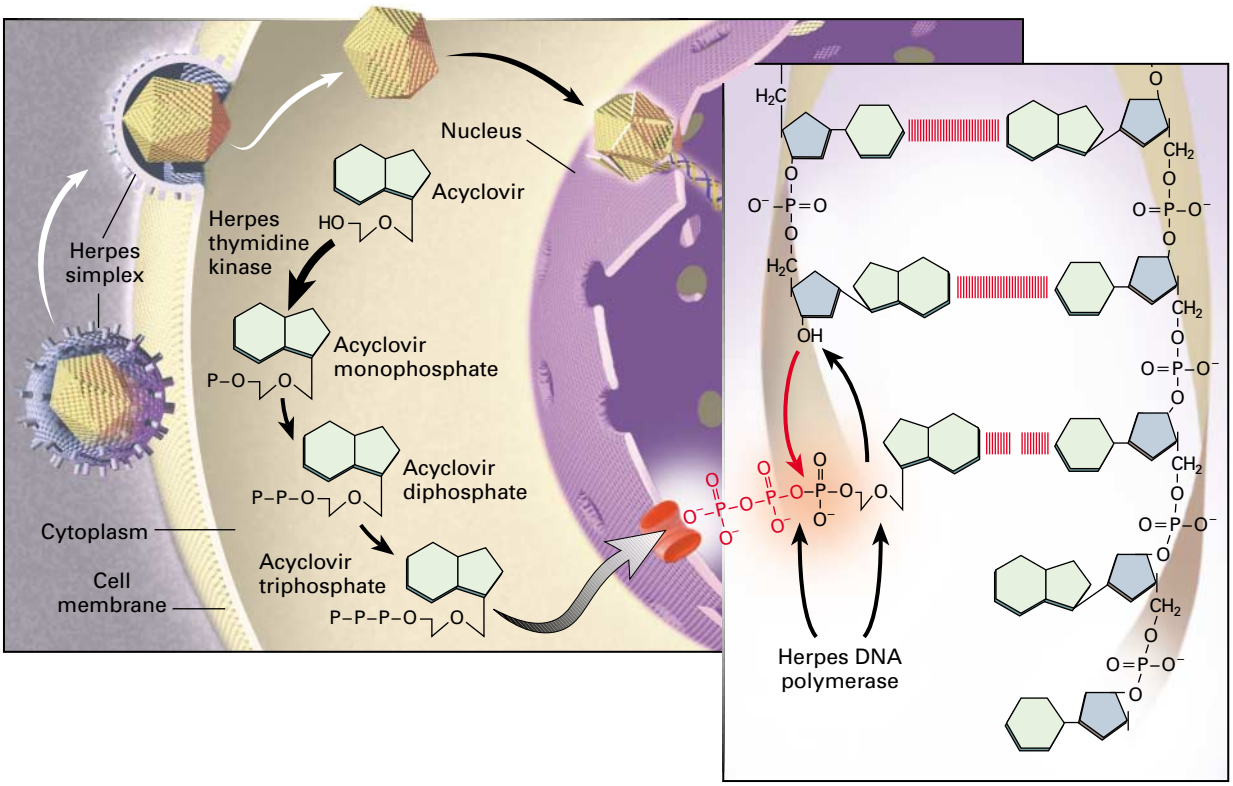

Figure 2. Mechanism of Action of Acyclovir in Cells Infected by Herpes Simplex Virus.

A herpes simplex virion is shown attaching to a susceptible host cell, fusing its envelope with the cell membrane, and releasing naked capsids that deliver viral DNA into the nucleus, where it initiates synthesis of viral DNA. Acyclovir molecules entering the cell are converted to acyclovir monophosphate by virus-induced thymidine kinase. Host-cell enzymes add two more phosphates to form acyclovir triphosphate, which is transported into the nucleus. After the 3′-terminal hydroxyl of the growing herpes simplex DNA chain cleaves pyrophosphate from acyclovir triphosphate (indicated by the red arrow in the inset), viral DNA polymerase inserts acyclovir monophosphate rather than 2′-deoxyguanosine monophosphate into the viral DNA (indicated by black arrows in the inset). Further elongation of the chain is impossible because acyclovir monophosphate lacks the 3′ hydroxyl group necessary for the insertion of an additional nucleotide, and the exonuclease associated with the viral DNA polymerase cannot remove the acyclovir moiety. In contrast, ganciclovir and penciclovir have a 3′ hydroxyl group; therefore, further synthesis of viral DNA is possible in the presence of these drugs. Foscarnet acts at the pyrophosphate-binding site of viral DNA polymerase and prevents cleavage of the pyrophosphate from nucleoside triphosphates, thus stalling further primer–template extension. The red bands between the viral DNA strands in the inset indicate hydrogen bonding of the base pairs.

been developed. All antiviral drugs, nevertheless, have the potential to cause adverse effects (Table 2), and some are unexplainable, such as the thrombotic microangiopathy associated with valacyclovir in patients with the acquired immunodeficiency syndrome.[58]

CURRENT ISSUES IN ANTIVIRAL THERAPY

The goals for treating acute viral infections in immunocompetent patients are to reduce the severity of the illness and its complications and to decrease the rate of transmission of the virus. Thus, safety and convenience of dosing are important attributes for an antiviral drug. The goal of antiviral therapy in patients with chronic viral infections, on the other hand, is to prevent viral damage to visceral organs, especially the liver, lungs, and gastrointestinal tract, and to the central nervous system. In this case, efficacy is of primary importance.

Antiviral drugs can be used for prophylaxis, suppression (to keep viral replication below the rate that causes tissue damage in asymptomatic but infected patients), preemptive therapy (triggered by qualitative or quantitative evidence of infection before symptoms become apparent), or treatment of overt disease. Because the efficacy of antiviral therapy is limited in immunocompromised patients, prophylactic or suppressive strategies become more important for these patients.

Genital Herpes

Three drugs are approved for the treatment of genital herpes infections: acyclovir, valacyclovir, and

famciclovir. Acyclovir is the only one available for intravenous administration. In a study of primary genital herpes infection, a 5-day course of intravenous acyclovir resulted in complete healing of lesions in an average of 9 days, as compared with 21 days in patients given placebo ($P=0.002$); the duration of pain was also shorter in the patients treated with acyclovir.[12] This therapy is practical only for patients who are ill enough to require hospitalization or who are willing to make frequent visits to an outpatient clinic.

In most patients with primary herpes infections and all those with recurrent infections, oral therapy is appropriate. For the treatment of first genital herpes infections, oral acyclovir or valacyclovir[59] is preferable to famciclovir on the basis of peer-reviewed data. Acyclovir is the treatment of choice for initial episodes of genital herpes in pregnant women, because it has been used more than the other drugs and seems safe.

For the treatment of recurrent infections, clinical trials have demonstrated that acyclovir, valacyclovir, and famciclovir have equivalent efficacy.[17,33,60] Generic acyclovir is usually less expensive than the other two drugs and therefore preferable. If the costs of the drugs are equivalent, however, the choice is between the safety record of acyclovir and having to take fewer daily doses of valacyclovir or famciclovir. For suppressive therapy, acyclovir has been used safely for longer periods and in many more patients than the other two drugs. However, there are no data to suggest that either valacyclovir or famciclovir at the doses recommended for the treatment of genital herpes has more adverse effects than acyclovir. Preclinical studies with famciclovir revealed carcinogenicity in laboratory animals, so some physicians are reluctant to use it for long-term suppression. Acyclovir ointment is approved for genital herpes, but most physicians do not recommend it because it is active only against superficial cutaneous lesions.

A hotly debated issue is whether suppressive therapy can reduce the transmission of genital herpes. In a study of 16 women with recurrent herpes infections, treatment with acyclovir decreased the number of days that herpes simplex virus DNA could be detected in genital tract specimens, but this effect was lost soon after the drug was discontinued, indicating that it must be continued indefinitely to prevent transmission.[61] Furthermore, the fact that the virus cannot be detected in the genital area by culture or molecular techniques does not prove that a patient is not infectious.

Mucocutaneous Herpes

Mucocutaneous herpes is debilitating in immunocompromised patients. The ability of intravenous acyclovir to suppress reactivation of mucocutaneous herpes simplex infections was first demonstrated in patients who had received bone marrow transplants.[62] A placebo-controlled trial subsequently found that a seven-day course of intravenous acyclovir accelerated healing by at least a week.[11] Thus, intravenous acyclovir is now considered the standard for the prevention and treatment of tissue-invasive herpes simplex virus infections in immunocompromised patients (Table 3). In a recent trial, penciclovir given intravenously in doses of 5 mg per kilogram of body weight every 8 or 12 hours was equivalent to intravenous acyclovir, and it may soon be available as an alternative.[63] For patients who do not require hospitalization, oral administration of valacyclovir, famciclovir, or acyclovir is acceptable for treatment and for the suppression of recurrences.

Recurrences of herpes labialis in otherwise healthy persons are short-lived, and the need for therapy is questionable. Penciclovir cream has been approved for recurrent orofacial herpes in immunocompetent patients.[64] For patients who begin therapy in the prodromal period or when the lesions are in the erythematous stage, oral acyclovir shortens the clinical illness by one to two days.[65] Acyclovir also reduced the rate of reactivation from 26 percent to 7 percent in a placebo-controlled study of 147 skiers who began suppressive therapy before exposure to the sun.[66]

Neonatal Herpes

Neonatal herpes infections are difficult to diagnose and treat. Intravenous acyclovir is the treatment of choice, but morbidity and mortality remain high except among infants whose disease is limited to the skin, eyes, or mouth.[67] Prolonged oral administration of acyclovir after initial treatment with intravenous acyclovir has been advocated, because infants who have more than three cutaneous recurrences in the first year of life have an increased risk of neurologic impairment.[67] In a small study, suppression of the virus with oral acyclovir prevented cutaneous recurrences but was associated with transient neutropenia.[68] Oral acyclovir suppressed symptomatic genital herpes in late pregnancy in a placebo-controlled study of 46 women but had no effect on viral shedding or fetal outcome.[69]

Herpes Encephalitis

Despite antiviral therapy, herpes encephalitis causes substantial morbidity and mortality, most likely because of the delay between the onset of disease and the initiation of therapy. The therapy of choice is intravenous acyclovir, which is most beneficial if given before the patient lapses into semicoma or coma.[70] In a study of 69 patients, 12 of the 32 patients (38 percent) who received acyclovir had only minor impairment or none at all, as compared with 5 of the 37 patients (14 percent) who received vidarabine ($P=0.02$).[70] Some physicians treat patients with herpes encephalitis for 21 days because of the possibility of late relapses.

Chickenpox

When treatment with acyclovir is begun within 24 hours after the appearance of rash, the duration and severity of chickenpox are decreased by 25 to 30 percent.[14,71,72] The rationale for treating all adolescents and adults is that chickenpox is more severe for them than it is for young children. In a comparison of children and adolescents (13 to 18 years of age) in the placebo groups of two nearly identical studies, the adolescents had more skin lesions ($P=0.003$) and higher constitutional-illness scores ($P=0.03$) than the children.[72] The rationale for treating children is that chickenpox is not always mild, and it is impossible to predict exactly which child is destined to have a severe case. Since acyclovir therapy is safe, the risk–benefit ratio favors treatment. Concern that widespread treatment will lead to the emergence of viral resistance or blunting of the immune response has been allayed by data to the contrary from controlled trials.[71]

Chickenpox can be life-threatening in neonates, children with leukemia, and recipients of transplants, all of whom should be treated with acyclovir. Most authorities recommend treatment for pregnant women, particularly during the second and third trimesters. Intravenously administered acyclovir prevents the spread of the virus to the visceral organs if given promptly.[73] In a study of eight immunocompromised children, the four who received acyclovir within two days after the onset of rash had uncomplicated chickenpox, whereas the four treated more than four days after the onset of rash had visceral disease.[74] Switching from intravenous to oral acyclovir is permissible once the fever has disappeared, provided there is no evidence of visceral chickenpox.[75]

Herpes Zoster

The compelling reason to treat herpes zoster with antiviral drugs is to prevent the severe lingering pain — postherpetic neuralgia — that is a common complication of the infection, especially among patients over 50 years of age. The problem is first how to define the pain and then how to quantify it objectively.[76] Acyclovir, valacyclovir, and famciclovir, if given within 72 hours after the onset of rash, accelerate cutaneous healing by an average of two days.[18,34,77] Valacyclovir is slightly more effective than acyclovir in alleviating zoster-associated pain. In a comparative trial, the median duration of pain was 38 days among 384 patients who received a 7-day course of valacyclovir, as compared with 51 days among 376 patients who were given acyclovir ($P=0.001$).[18] With respect to convenience of dosing and efficacy, valacyclovir and famciclovir are preferable to acyclovir (Table 3).

Patients over the age of 50 years should be offered antiviral therapy, because they are at the highest risk for postherpetic neuralgia. Younger patients should be considered for treatment if they present with moderate-to-severe pain. Patients of any age with ophthalmic zoster should receive antiviral therapy, because they can lose their vision if not treated. Oral acyclovir reduces the incidence and severity of ocular complications, especially anterior uveitis, when begun as late as seven days after the onset of rash.[78]

A long-standing debate has been whether to use glucocorticoids in patients with acute herpes zoster. The results of two recent trials in which all patients received acyclovir were similar; as compared with placebo, oral glucocorticoid therapy accelerated the healing of skin lesions by two days, or 10 percent of the total healing time, but did not reduce the incidence of postherpetic neuralgia.[79,80] Nevertheless, the use of glucocorticoids remains controversial; the potential for adverse events must be weighed against the short-term quality-of-life benefit they provide when given in conjunction with antiviral therapy.

In immunocompromised patients, intravenously administered acyclovir prevents both cutaneous and visceral dissemination of zoster, even when therapy is initiated as late as six days after the onset of rash.[13] Valacyclovir and famciclovir are logical alternatives for patients with moderate immunosuppression and localized herpes zoster.

Respiratory Virus Infections

Amantadine and rimantadine reduce the severity and shorten the duration of influenza A infections if given to otherwise healthy adults within 48 hours after the onset of illness.[49,81] Whether these drugs can prevent the complications of influenza is not known. Both amantadine and rimantadine also provide effective prophylaxis against influenza A.[50] Rimantadine is preferable to amantadine because it has fewer adverse effects (Table 2), but it is also more expensive.

Although placebo-controlled trials have reported that aerosolized ribavirin is effective in infants hospitalized for severe lower respiratory tract infections caused by respiratory syncytial virus,[82] this therapy has become controversial because of concern about cost, convenience, and the accuracy of these results.[83] Passive prophylaxis with immune globulin is a useful approach for infants at high risk — for example, those born prematurely, those with bronchopulmonary dysplasia, or those meeting both conditions. In a placebo-controlled trial involving 510 premature infants with bronchopulmonary dysplasia, monthly treatment with respiratory syncytial virus immune globulin during the season when most respiratory virus infections occur significantly decreased the rate and duration of hospitalization for infections caused by this virus.[84] Respiratory viruses are usually more pathogenic for immunocompromised patients, but antiviral therapies for influenza A and respiratory syncytial virus infections are the same as those prescribed for immunocompetent patients.[85,86]

Hepatitis

The treatment of chronic hepatitis B, C, and D was recently reviewed in the *Journal*.[87] Several preparations of interferon alfa have been approved for the treatment of these infections. Sustained clinical or virologic responses occur in only about 33 percent of patients with chronic hepatitis B or C who are given interferon alfa alone, and most have a relapse after therapy is discontinued.

There are two promising recent developments for the treatment of chronic hepatitis. Lamivudine has proved beneficial in patients with chronic hepatitis B[88,89] and is now approved for this indication (Table 3). The other important development is the combination of interferon alfa and ribavirin as a therapy for chronic hepatitis C. Twenty-four weeks of treatment resulted in a sustained virologic remission (as measured by serum hepatitis C virus RNA) in 18 of 50 patients assigned to combination therapy, as compared with 9 of 50 patients assigned to monotherapy with interferon alfa ($P=0.05$).[44]

Cytomegalovirus Disease

Cytomegalovirus disease responds to treatment with either foscarnet or ganciclovir.[24,36] Most physicians prefer ganciclovir because of the potential side effects of foscarnet, but these can be obviated or minimized with maintenance of hydration and electrolyte balance[90] (Table 2). The quantity of cytomegalovirus in the blood determines the extent of tissue damage,[91] and therefore the duration of treatment should be guided by repeated measurements of cytomegalovirus in blood samples. Retreatment is necessary in approximately one third of patients.

Cytomegalovirus disease is associated with high morbidity, especially among recipients of bone marrow transplants, making prevention an important priority. However, there is no consensus on the optimal preventive regimen, because the results vary according to the underlying disease and the intensity of the immunosuppressive regimen. Significant reductions in the incidence of cytomegalovirus disease have been reported with the use of oral acyclovir among recipients of renal allografts,[15] intravenous ganciclovir among recipients of bone marrow, liver, and heart transplants,[20] intravenous acyclovir followed by oral acyclovir among recipients of bone marrow transplants,[92] and oral ganciclovir among recipients of liver transplants.[28]

The duration of prophylaxis has varied widely, but the consensus is that it should be given for at least three months (Table 3). A three-month course of valacyclovir has recently been reported to be efficacious in recipients of renal allografts.[93] Another approach, termed preemptive therapy, is to begin antiviral drugs when evidence of active (or increasing) cytomegalovirus replication is documented, but before symptoms develop.[27]

Viral Resistance

Strains of influenza A with point mutations that alter the amino acid sequence of the M2 protein and thus render them resistant to amantadine and rimantadine have been transmitted between members of a household,[94] but the danger, if any, that these strains pose to the general population is not known. In contrast, mutant strains of herpes group viruses that are resistant, usually because they do not induce phosphorylation of guanosine nucleosides (Fig. 2), have caused serious illness in immunocompromised patients.[95,96]

Viral resistance should be suspected when patients — almost exclusively those who are immunosuppressed — have no response to appropriate doses of antiviral drugs within five to seven days. If virologic testing is possible, phenotypic or genotypic analysis of a culture should be performed. Cultures of lesions are preferred in the case of patients with mucocutaneous herpes, herpes zoster, or chickenpox. Blood treated with anticoagulants is the specimen of choice from patients with cytomegalovirus disease. Data on in vitro susceptibility are usually available within two weeks to guide the choice of alternative therapies. Genotypic analysis can theoretically be done more quickly, but assays for mutations causing drug resistance are not yet widely available. In the absence of such tests, foscarnet is the drug of choice for infections with herpes simplex virus and varicella–zoster virus that do not respond to acyclovir and for cytomegalovirus infections that do not respond to ganciclovir.

FUTURE DIRECTIONS

Seven of the 11 antiviral drugs reviewed are nucleoside analogues. Two others — amantadine and rimantadine — are similar to each other in structure and activity. Clearly, new drugs with different structures and mechanisms of action are needed. An exciting advance in drug therapy has been the computer-aided design of molecules that precisely inactivate viral enzymes or receptors. Successful drugs such as zanamivir, an inhibitor of influenza A and B neuraminidases, are being developed with the use of this approach.[97,98] Recent progress in antiviral research includes the discovery of inhibitors of herpesvirus proteases[99] and the development of new drugs for the management of cytomegalovirus, including a valine ester of ganciclovir; cidofovir, a pyrimidine nucleotide; and fomivirsen, an antisense oligonucleotide.[100]

The potential of antiviral therapy has not yet been realized, especially for the management of chronic viral infections. Lessons learned from antiretroviral therapy serve as a primer for the following predictions. The clinical diagnosis of viral disease will be confirmed more swiftly with the use of quantitative molecular techniques, which in turn will permit ear-

lier intervention and can be used to monitor therapeutic success; and combinations of drugs will be given, especially for the treatment of chronic viral infections. Combination therapy will decrease the rate of emergence of resistant viruses and may also result in pharmacologic interactions that improve the distribution and concentration of antiviral drugs in infected cells.

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