Fomivirsen has been approved for intravitreal administration in the treatment of CMV retinitis in AIDS patients who have failed to respond to other treatments or cannot tolerate them. Injections of 330 mg for two doses 2 weeks apart, followed by maintenance doses of 330 mg monthly, significantly reduce the rate of progression of CMV retinitis. The major toxicity is ocular inflammation, including vitritis and iritis, which usually responds to topically administered glucocorticoids.

GANCICLOVIR AND VALGANCICLOVIR

An analogue of acyclovir, ganciclovir is active against HSV and VZV and is markedly more active than acyclovir against CMV. Ganciclovir triphosphate inhibits CMV DNA polymerase and can be incorporated into CMV DNA, whose elongation it eventually terminates. In HSV- and VZV-infected cells, ganciclovir is phosphorylated by virus-encoded thymidine kinases; in CMV-infected cells, it is phosphorylated by a viral kinase encoded by the UL97 gene. Ganciclovir triphosphate is present in tenfold higher concentrations in CMV-infected cells than in uninfected cells. Ganciclovir is approved for the treatment of CMV retinitis in immunosuppressed patients and for the prevention of CMV disease in transplant recipients. It is widely used for the treatment of other CMV-associated syndromes, including pneumonia, esophagogastrointestinal infections, hepatitis, and "wasting" illness.

Ganciclovir is available for IV or oral administration. Because its oral bioavailability is low (5–9%), relatively large doses (1 g three times daily) must be administered by this route. Oral ganciclovir has largely been supplanted by valganciclovir, which is the L-valyl ester of ganciclovir. Valganciclovir is well absorbed orally, with a bioavailability of 60%, and is rapidly hydrolyzed to ganciclovir in the intestine and liver. The area under the curve for a 900-mg dose of valganciclovir is equivalent to that for 5 mg/kg of IV ganciclovir, although peak serum concentrations are ~40% lower for valganciclovir. The serum half-life is 3.5 h after IV administration of ganciclovir and 4.0 h after PO administration of valganciclovir. Ganciclovir is excreted primarily by the kidneys in an unmetabolized form, and its dosage should be reduced in cases of renal failure. Ganciclovir therapy at the most commonly used initial IV dosage—i.e., 5 mg/kg every 12 h for 14–21 days—can be changed to valganciclovir (900 mg PO twice daily) when the patient can tolerate oral therapy. The maintenance dose is 5 mg/kg IV daily or five times per week for ganciclovir and 900 mg by mouth once a day for valganciclovir. Dose adjustment in patients with renal dysfunction is required. Intraocular ganciclovir, given by either intravitreal injection or intraocular implantation, has also been used to treat CMV retinitis.

Ganciclovir is effective as prophylaxis against CMV-associated disease in organ and bone marrow transplant recipients. Oral ganciclovir administered prophylactically to AIDS patients with CD4+ T cell counts of <100/μL has provided protection against the development of CMV retinitis. However, the long-term benefits of this approach to prophylaxis in AIDS patients have not been established, and most experts do not recommend the use of oral ganciclovir for this purpose. As already mentioned, valganciclovir has supplanted oral ganciclovir in settings where oral prophylaxis or therapy is considered.

The administration of ganciclovir has been associated with profound bone marrow suppression, particularly neutropenia, which significantly limits the drug's use in many patients. Bone marrow toxicity is potentiated in the setting of renal dysfunction and when other bone marrow suppressants, such as zidovudine or mycophenolate mofetil, are used concomitantly.

Resistance has been noted in CMV isolates obtained after therapy with ganciclovir, especially those from patients with AIDS or from patients receiving prolonged ganciclovir therapy after organ transplantation. Such resistance may develop through a mutation in either the viral UL97 gene or the viral DNA polymerase. Ganciclovir-resistant isolates are usually sensitive to foscarnet (see below) or may be sensitive to cidofovir, depending on the mechanism of resistance (see above).

FAMCICLOVIR AND PENCICLOVIR

Famciclovir is the diacetyl 6-deoxyester of the guanosine analogue penciclovir. This agent is well absorbed orally, has a bioavailability of 77%, and is rapidly converted to penciclovir by deacetylation and oxidation in the intestine and liver. Penciclovir's spectrum of activity and mechanism of action are similar to those of acyclovir. Thus, penciclovir usually is not active against acyclovir-resistant viruses. However, some acyclovir-resistant viruses with altered thymidine kinase or DNA polymerase substrate specificity may be sensitive to penciclovir. This drug is phosphorylated initially by a virus-encoded thymidine kinase and subsequently by cellular kinases to penciclovir triphosphate, which inhibits HSV-1, HSV-2, VZV, and EBV as well as hepatitis B virus (HBV). The serum half-life of penciclovir is 2 h, but the intracellular half-life of penciclovir triphosphate is 7–20 h—markedly longer than that of acyclovir triphosphate. The latter is the basis for the less frequent (twice-daily) dosing schedule for famciclovir than for acyclovir. Penciclovir is eliminated primarily in the urine by both glomerular filtration and tubular secretion. The usually recommended dosage interval should be adjusted for renal insufficiency.

Clinical trials involving immunocompetent adults with herpes zoster showed that famciclovir was superior to placebo in eliciting the resolution of skin lesions and virus shedding and in shortening the duration of postherpetic neuralgia; moreover, administered at 500 mg every 8 h, famciclovir was at least as effective as acyclovir administered at an oral dose of 800 mg five times daily. Famciclovir was also effective in the treatment of herpes zoster in immunosuppressed patients. Clinical trials have demonstrated its effectiveness in the suppression of genital HSV infections for up to 1 year and in the treatment of initial and recurrent episodes of genital herpes. Famciclovir is effective as therapy for mucocutaneous HSV infections in HIV-infected patients. Application of a 1% penciclovir cream reduces the duration of signs and symptoms of herpes labialis in immunocompetent patients (by 0.5–1 day) and has been approved for that purpose by the FDA. Famciclovir is generally well tolerated, with occasional headache, nausea, and diarrhea reported in frequencies similar to those among placebo recipients. The administration of high doses of famciclovir for 2 years was associated with an increased incidence of mammary adenocarcinomas in female rats, but the clinical significance of this effect is unknown.

FOSCARNET

Foscarnet (phosphonoformic acid) is a pyrophosphate-containing compound that potently inhibits herpesviruses, including CMV. This drug inhibits DNA polymerases at the pyrophosphate binding site at concentrations that have relatively little effect on cellular polymerases. Foscarnet does not require phosphorylation to exert its antiviral activity and is therefore active against HSV and VZV isolates that are resistant to acyclovir because of deficiencies in thymidine kinase as well as against most ganciclovir-resistant strains of CMV. Foscarnet also inhibits the reverse transcriptase of HIV and is active against HIV in vivo.

Foscarnet is poorly soluble and must be administered intravenously via an infusion pump in a dilute solution over 1–2 h. The plasma half-life of foscarnet is 3–5 h and increases with decreasing renal function because the drug is eliminated primarily by the kidneys. It has been estimated that 10–28% of a dose may be deposited in bone, where it can persist for months. The most common initial dosage of foscarnet—60 mg/kg every 8 h for 14–21 days—is followed by a maintenance dose of 90–120 mg/kg once a day.

Foscarnet is approved for the treatment of CMV retinitis in patients with AIDS and of acyclovir-resistant mucocutaneous HSV infections. In a comparative clinical trial, the drug appeared to be about as efficacious as ganciclovir against CMV retinitis but was associated with a longer survival period, possibly because of its activity against HIV. Intraocular foscarnet has been used to treat CMV retinitis. In addition, foscarnet has been employed to treat acyclovir-resistant HSV and VZV infections as well as ganciclovir-resistant CMV infections, although resistance to foscarnet has been reported in CMV isolates obtained during therapy. Foscarnet has also been used to treat HHV-6 infections in immunosuppressed patients.

The major form of toxicity associated with foscarnet is renal impairment. Thus renal function should be monitored closely, particularly during the initial phase of therapy. Because foscarnet binds divalent metal ions, hypocalcemia, hypomagnesemia, hypokalemia,