Herpesviruses

Paul D Griffiths

Abstract

Herpesviruses are highly successful viruses because they transmit to many individuals in all populations, often without causing obvious symptoms. However, they are responsible for significant diseases, including herpes simplex encephalitis, genital herpes, chickenpox, infectious mononucleosis, cytomegalic inclusion disease, exanthem subitum and Kaposi's sarcoma. They also cause severe opportunistic disease in patients with T-cell immunodeficiency. Antiviral drugs have greatly reduced the burden of disease caused by herpesviruses. Aciclovir and penciclovir (with their pro-drugs valaciclovir and famciclovir, respectively) are safe in clinical practice. Ganciclovir (and its pro-drug valganciclovir) and foscarnet have significant toxic effects but are clearly indicated for either pre-emptive therapy or prophylaxis of the immunocompromised host. Ganciclovir is indicated for neonates born with CNS symptoms of congenital cytomegalovirus (CMV) infection. Better drugs are required for CMV, but maribavir failed at Phase 3 evaluation. A live attenuated vaccine for varicella-zoster virus (VZV) has already reduced the incidence of chickenpox and deaths from chickenpox following universal immunization in the USA. Subunit and DNA plasmid vaccines for CMV have shown encouraging Phase 2 results while one herpes simplex virus vaccine failed a Phase 3 evaluation. Vaccines for VZV and CMV can boost natural immunity.

Keywords antiviral drugs; herpesvirus; natural history; pathogenesis; treatment; vaccines

What's new?

- A randomized trial is now comparing 6 weeks' vs. 6 months' treatment with valganciclovir for cases of congenital cytomegalovirus (CMV) presenting with symptoms
- Two CMV vaccines show promise
- These two CMV vaccines, like varicella-zoster virus, can boost natural immunity
- A herpes simplex virus vaccine failed a Phase 3 evaluation
- Maribavir failed a Phase 3 evaluation against CMV

The herpesviruses are diverse and there are major differences between members of the group; however, they also have many features in common (Table 1).

Pathogenesis

The pathogenesis of diseases caused by herpesviruses is complex with several possible mechanisms.

- Disease can result from the virus replicating in cells and destroying them by lysis (e.g. chickenpox).
- An immunologically mediated disease can develop from the host immune response to a herpesvirus; for example, cytomegalovirus (CMV) vitritis, erythema multiforme triggered by herpes simplex virus (HSV) reactivation, or CMV-driven immunosenescence.[1]
- The virus can precipitate rearrangements of host chromosomes, so activating endogenous oncogenes to produce a malignant phenotype (e.g. Epstein–Barr virus (EBV), Burkitt's lymphoma).

Because herpesviruses interact in multiple ways with the host, each virus can cause more than one disease (Table 2). In general, disease is more common and more severe in patients with T-cell immunodeficiency; this part of the immune response must therefore be responsible for controlling herpesvirus replication, and herpesviruses are major pathogens in transplant patients and those with AIDS.

Antiviral agents

Study of herpesvirus replication has identified essential virus-encoded enzymes. Specific inhibitors of these act as antiviral agents.

Aciclovir was the first antiviral agent to be licensed. It is effective and without significant side effects, and remains the standard therapy against which newer drugs are compared.

The specificity of aciclovir is achieved because the phosphorylation required for its activation occurs only in cells infected with herpesviruses. In the case of HSV and varicella-zoster virus (VZV), the viral thymidine kinase enzyme phosphorylates aciclovir. CMV does not have a thymidine kinase, but the product of its *UL97* gene performs the same function. Human herpesvirus (HHV) types 6 and 7 also have homologues of *UL97*. Aciclovir monophosphate is further phosphorylated to the triphosphate by cellular enzymes; the triphosphate becomes incorporated into the growing DNA chain and acts as an obligate chain terminator, inhibiting the DNA polymerase of all herpesviruses. Aciclovir is generally non-toxic, but is excreted through the kidneys and dosage intervals should be increased in patients with renal failure (see *BNF* or equivalent national formulary).

Ganciclovir and penciclovir are activated in a similar manner, but their triphosphates exhibit important differences in safety profiles, partly because they are not obligate chain terminators. Ganciclovir can be incorporated into host DNA and is carcinogenic and teratogenic in animals. It causes clinically significant bone marrow suppression and is licensed only for CMV infections that are life-threatening or sight-threatening. In contrast to ganciclovir, penciclovir is well tolerated clinically.

Paul D Griffiths ***MD DSc FRCPath*** *is a Professor of Virology at University College London Medical School, UK.* *Conflicts of interest: PDG has attended advisory boards for all pharmaceutical companies developing antiviral drugs against herpesviruses. In the last five years this has included the manufacturers of licensed compounds (Roche, Novartis) and those in development (Viropharma, Chimerix, AiCuris, Astellas, Boehringer-Mannheim, Microbiotix). The intention in giving advice to all in the field has been to avoid any conflict of interest by association with any one company.*

Characteristics of herpesviruses

- Large dsDNA genome
- Characteristic appearance on electron microscopy
- Initial infection often asymptomatic
- Establish latency, persist for life of individual
- Reactivate from latency
- Most reactivations are asymptomatic
- Re-infections also occur
- Most herpesviruses cause more than one disease
- Interfere with immune responses

Table 1

Pro-drugs: the bioavailability of the above compounds is poor when administered orally. This can be improved by the use of pro-drugs, which are absorbed and then metabolized in the intestinal wall and/or liver to produce high plasma concentrations of the parent compound. Famciclovir is the pro-drug of penciclovir, valaciclovir of aciclovir, and valganciclovir of ganciclovir. After activation by viral thymidine kinase, penciclovir triphosphate persists intracellularly for significantly longer than does aciclovir triphosphate, yet the latter is a more potent inhibitor of DNA polymerase. The newer pro-drugs are replacing aciclovir for many indications (Table 3).

Alphaherpesviruses

HSV-1 is spread readily within families by salivary contact. Primary infection can cause stomatitis (Figure 1), but is usually asymptomatic. The virus establishes latency in the dorsal root ganglia supplying the trigeminal nerve. Reactivation of the viral genome can be caused by ultraviolet light, stress or menstruation. Centrifugal axonal passage of virus components may be perceived by the patient as a prodromal tingling, typically occurring 24 hours before vesicular eruption on the oral skin. HSV replicates in the skin for 1–3 days, after which new epithelial cells migrate from the edge of the lesion to repair the damage.

In patients with eczema, scratching can introduce the virus at multiple sites, causing a chickenpox-like rash termed 'eczema herpeticum'. This should be treated with aciclovir, 800 mg orally five times per day; the drug can be given intravenously in patients with clinically severe rash.

HSV-2 is the main cause of primary and genital herpes. Note that many cases of primary genital herpes are caused by HSV-1 through oral-genital sex, though this virus is less likely to reactivate from the sacral ganglia than is HSV-2.

Prompt treatment for only 24 hours at the prodromal stage may abort a recurrent attack,[2] but antiviral treatment has only a modest effect if it is begun after the vesicles have formed. Therefore, if treatment is required, it should be given orally (not

Major diseases caused by herpesviruses

	Patients with normal immunity			Immunocompromised
	Children	**Adults**	**Elderly**	
Alphaherpesviruses				
Herpes simplex virus 1	Stomatitis[a] Encephalitis[a]	Cold sores[b] Keratitis[b] Encephalitis[b] Erythema multiforme[b] Primary genital herpes[a]		Dissemination[b]
Herpes simplex virus 2	Encephalitis[a]	Primary genital herpes[a] Recurrent genital herpes[b]		Dissemination[b]
Varicella-zoster virus	Chickenpox[a]	Shingles[b]	Shingles[b]	Dissemination[b]
Betaherpesviruses				
Cytomegalovirus	Congenital[a]	Infectious mononucleosis[a]	Immunosenescence	Pneumonitis[b] Retinitis[b] Enteritis[b]
Human herpesvirus 6	Roseola infantum[a] Febrile fits[a]			Encephalitis[b]
Human herpesvirus 7	Roseola infantum[a]			
Gammaherpesviruses				
Epstein–Barr virus		Infectious mononucleosis[a]		Lymphoma[b]
Human herpesvirus 8			Kaposi's sarcoma[b]	Kaposi's sarcoma[b]

[a] Diseases caused by primary infection.
[b] Diseases caused by reactivated herpesviruses (some may also occur with primary infection).

Table 2