CPD/CME

Link to this article online for CPD/CME credits

THERAPEUTICS

Antivirals for herpes simplex viruses

Shailendra Sawleshwarkar,[1] Dominic E Dwyer[2]

[1]Western Sydney Sexual Health Centre, University of Sydney, Parramatta, NSW, 2150, Australia
[2]Institute of Clinical Pathology and Medical Research and University of Sydney, Westmead Hospital, Westmead, NSW 2145, Australia
Correspondence to: S Sawleshwarkar shailendra.sawleshwarkar@sydney.edu.au

Cite this as: *BMJ* 2015;351:h3350
doi: 10.1136/bmj.h3350

This is one of a series of occasional articles on therapeutics for common or serious conditions, covering new drugs and old drugs with important new indications or concerns. The series advisers are Robin Ferner, honorary professor of clinical pharmacology, University of Birmingham and Birmingham City Hospital, and Albert Ferro, professor of cardiovascular clinical pharmacology, King's College London. To suggest a topic, please email us at practice@bmj.com

A 25 year old woman presents to her general practitioner with a two day history of painful vulval lesions. She has not had previous episodes and does not have any significant previous medical history. She is in a new relationship with a male partner. Genital examination shows multiple vulval ulcers.

What diseases are caused by herpes simplex viruses?

Herpes simplex viruses type 1 and type 2 (HSV-1 and HSV-2) commonly cause mucocutaneous disease, including orolabial infections (more commonly HSV-1; for example, gingivostomatitis and "cold sores") and genital herpes (HSV-2 or HSV-1).[1] Infections may be asymptomatic (see box for classification). Other important manifestations include perinatal infection following symptomatic or asymptomatic maternal genital infection, encephalitis in children and adults, other neurological conditions (radiculitis, myelitis, and meningitis), eye disease (corneal ulceration, keratitis, iridocyclitis, acute retinal necrosis), and disseminated infections. This review will focus on use of antivirals in orolabial, genital, and neurological HSV infections.

What are antiviral drugs for HSV infections?

The nucleoside analogues aciclovir, valaciclovir (an aciclovir pro-drug), penciclovir, and famciclovir (a penciclovir pro-drug) are used for treatment, suppression, and prevention of initial and recurrent HSV infections. Both aciclovir and penciclovir competitively inhibit viral DNA polymerase.

Common indications for treatment include acute genital herpes and herpes labialis, as well as any form of neonatal or adult HSV encephalitis or other severe illness. Mucocutaneous HSV infections are commonly treated with oral antiviral agents, whereas intravenous aciclovir is used in encephalitis and severe HSV infections requiring hospital admission; newer antivirals have better bioavailability and less frequent dosing.[2 3]

CLASSIFICATION OF GENITAL AND LABIAL HERPES INFECTION

Primary infection—Recently acquired HSV-1 or HSV-2 infection in previously HSV-1 and HSV-2 seronegative people; these are generally more severe, are associated with constitutional symptoms, and last longer than non-primary infections

Non-primary infection—Recently acquired infection in which the patient is seronegative to the infecting HSV type but seropositive to the other; these tend to be less severe than primary infections

First episode infection—First clinically apparent episode of genital herpes; may be primary or non-primary, or can be the first clinical recurrence of a past infection

Recurrent infection—Clinically evident HSV-1 or HSV-2 disease in a patient with previous HSV-1 or HSV-2 infection (and HSV type specific antibodies); generally less severe than primary or first episodes and more frequent in the six months following a primary infection

Asymptomatic viral shedding—Laboratory detection of HSV from skin or mucosa in the absence of clinical lesions

THE BOTTOM LINE

- Aciclovir, valaciclovir, and famciclovir are similarly effective in healing lesions, and in reducing duration of symptoms and of viral shedding, in genital herpes
- Long term suppressive treatment is safe and effectively reduces recurrences in genital and orolabial herpes; however, it does not completely eliminate recurrences or risk of transmission of genital herpes simplex virus infection to sexual partners
- In older patients, and those with impaired renal function or taking nephrotoxic drugs, monitor renal function closely and consider using lower doses; owing to the risk of renal toxicity, intravenous aciclovir requires good hydration
- Suppressive aciclovir or valaciclovir in the last weeks of pregnancy reduces clinical disease in the mother and transmission to the baby at the time of delivery but does not completely eliminate the risk of neonatal transmission
- Neonates with central nervous system infection require high dose intravenous aciclovir for 21 days, and suppressive treatment with valaciclovir improves neurodevelopmental outcomes

How well do these antivirals work?

Treatment of initial and recurrent episodes of genital herpes

Large randomised controlled trials and systematic reviews confirm the efficacy of oral aciclovir, valaciclovir, and famciclovir in both treating and preventing recurrences of genital herpes. A randomised controlled trial in women with recurrent genital herpes found that, compared with placebo, oral aciclovir resulted in 1.48-fold (mean 5.1 *v* 6.0 days; P=0.098) greater likelihood of healing of all lesions and 1.88-fold (mean 3.0 *v* 5.0 days; P=0.008) greater likelihood of cessation of HSV shedding.[4] In a randomised controlled trial in primary genital herpes, efficacy of valaciclovir and aciclovir did not differ significantly in duration of viral shedding or time to healing.[3] A double blind, parallel group study of short course treatment for recurrent genital herpes showed similar time to healing of lesions in patients taking single day famciclovir and three day valaciclovir (median 4.25 *v* 4.08 days; hazard ratio 1.08, 95% confidence interval 0.88 to 1.32).[2] Although few randomised controlled trials have directly compared famciclovir and valaciclovir for treating genital herpes, published data comparing these with placebo or aciclovir do not suggest significant difference in efficacy.

Suppressive treatment for genital herpes

Suppressive treatment for genital herpes involves patients taking daily oral antivirals to reduce recurrences.

thebmj.com

Previous articles in this series

- Drug treatment for adults with HIV infection (*BMJ* 2015;350:h1555)
- Mosquito repellents for travellers (*BMJ* 2015;350:h99)
- Grass pollen immunotherapy for treatment of allergic rhinitis (*BMJ* 2014;349:g6586)
- Novel drugs and drug combinations for treating tuberculosis (*BMJ* 2014;349:g5948)
- Drug treatment of adults with nausea and vomiting in primary care (*BMJ* 2014;349:g4714)

In a recent Cochrane review of the efficacy of antivirals to suppress recurrences of genital herpes, suppressive therapy with aciclovir, valaciclovir, or famciclovir in patients experiencing at least four recurrences a year decreased the number of patients having at least one recurrence compared with placebo.[5] It also showed no difference in efficacy between these agents (table).[5] In a randomised placebo controlled trial, valaciclovir reduced the acquisition of genital herpes in serodiscordant couples from 3.6% in the placebo group to 1.9% in the valaciclovir group during an eight month follow-up.[6] Suppressive therapy reduces symptomatic and asymptomatic viral shedding but does not completely eliminate recurrences or chance of sexual transmission.[5 6]

Initial and recurrent episode of labial herpes

A systematic review examining treatment for first and recurrent attacks of herpes labialis concluded that oral antivirals may reduce the duration of pain and time to healing.[7] The review also found limited evidence that topical antiviral agents reduce pain and healing time in recurrent attacks and that topical agents are of marginal clinical importance.[7] A one day course of famciclovir or valaciclovir offers greater convenience and cost effectiveness compared with the usual five to seven days' treatment.[6] The table lists antivirals used in prevention of recurrences or for suppression of HSV in labial and genital herpes, along with the numbers needed to prevent.[8]

Randomised controlled trials show that short course, high dose regimens are as effective as longer treatment courses for genital and oral herpes.[1 7]

HSV in HIV co-infected and other immunosuppressed patients

HSV infection in people with HIV infection (in the absence of immune reconstitution caused by HIV therapy) and in recipients of solid organ and bone marrow transplants may be severe and prolonged and may cause disseminated disease. Patients with advanced immunodeficiency may need higher doses and longer duration of antivirals. In a large randomised placebo controlled study, in which only one of the partners was HIV-1 seropositive, daily aciclovir suppression therapy reduced the occurrence of HSV-2 genital ulcers by 73% (but not the risk of HIV-1 transmission).[9] In a Cochrane review of HSV prevention in patients receiving cancer treatment, aciclovir was found to be effective in preventing oral lesions (risk ratio 0.16, 0.08 to 0.31) or detection of viral isolates (0.17, 0.07 to 0.37).[10]

Neonatal herpes treatment and prevention

Neonates with HSV encephalitis need high dose intravenous aciclovir for at least 21 days to minimise the chance of relapse.[11] Infants with central nervous system disease who received suppressive aciclovir had better neurodevelopmental outcomes compared with the placebo group, and infants with central nervous system and skin, eyes, and mouth disease had less frequent skin recurrences while receiving suppressive therapy.[12] Suppressive aciclovir or valaciclovir in the last weeks of pregnancy reduces both clinical disease in the mother at the time of delivery and associated caesarean section rates but does not completely eliminate the risk of neonatal transmission.[13]

HSV encephalitis and other neurological conditions in adults

Intravenous aciclovir has been shown to be effective in HSV encephalitis in adults.[14] No controlled trials have been reported for acute treatment of HSV meningitis and radiculitis, which are treated with intravenous aciclovir or oral valaciclovir. Suppressive treatment with valaciclovir was not shown to prevent recurrence of meningitis in a randomised placebo controlled trial.[15]

HSV drug resistance

Clinical therapeutic failure is usually the result of delayed treatment, reduced drug absorption, poor adherence, and occasionally viral resistance. The prevalence of HSV nucleoside analogue resistance is less than 1% in immunocompetent patients but is more frequent (3.5-10%) in immunosuppressed patients, usually in those who have previously received prolonged therapy.[16] Confirmation of HSV resistance requires specialised viral genotypic or phenotypic testing. Treatment of such infections is usually with the pyrophosphate analogue foscarnet or the nucleoside phosphonate analogue cidofovir.

How safe are antivirals for HSV?

Large clinical trials evaluating oral aciclovir, famciclovir, and valaciclovir for treatment of various HSV infections indicate that these agents are generally well tolerated and have minimal adverse effects, even with prolonged oral treatment. Headaches, nausea and vomiting, dizziness, and abdominal pain are the most commonly reported adverse effects. In randomised controlled trials evaluating aciclovir, valaciclovir, and famciclovir, reports ranged from 4% to 13% for headache and from 5% to 6% for nausea.[2 3] Acute kidney

Antivirals for herpes simplex virus suppression or prevention of recurrences

Condition	Drug	Supporting evidence	Number needed to prevent (95% CI)
Recurrent genital herpes: suppressive treatment	Oral aciclovir	Systematic review of 22 randomised controlled trials[5]	2.4 (2.2 to 2.6)*
	Oral valaciclovir		2.3 (2.0 to 2.6)*
	Oral famciclovir		2.7 (2.2 to 3.5)*
Recurrent herpes labialis: prevention of recurrences	Oral aciclovir	Systematic review[8]	7.0 (4.5 to 15.6)†
	Oral valaciclovir		4.5 (2.4 to 40.5)†
HSV prevention in cancer patients	Oral aciclovir	Systematic review[10]	3 (2 to 3)‡

*≥1 clinical recurrence over treatment period ranging from 2 to 12 months.
†Recurrence of HSV-1 lesions during antiviral treatment when taken before appearance of any symptoms or exposure to triggers.
‡HSV oral lesions compared with placebo.

TIPS FOR PATIENTS

- Genital and labial herpes is usually diagnosed from the clinical symptoms and requires antiviral treatment; there are no significant differences in the efficacy of the available antivirals
- Episodic treatment for recurrent genital herpes needs to be started early, usually within 24 hours, and preferably by the patient
- Suppressive treatment for genital herpes is useful if recurrences are frequent (more than 4-6 a year), but it does not completely eliminate recurrences and the chance of transmission to sexual partners
- Long term treatments for prevention of recurrences of labial and genital herpes are generally safe; headache is the most common side effect
- Regular (every 6-12 months) review of suppressive therapy will allow discussion about possible discontinuation

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

We gave a draft of this article to two patients and asked them to give their opinion on the tips for patients. We made modifications to make the tips easier to understand, omitting more scientific terms.

injury due to reversible, crystal induced nephropathy may occur with intravenous aciclovir, particularly in older patients; this generally improves with hydration, and famciclovir has been used in patients with aciclovir induced renal toxicity. In a population based study, aciclovir or valaciclovir use was not associated with a higher risk of hospital admission with acute kidney injury compared with famciclovir (0.27% with aciclovir or valaciclovir versus 0.28% with famciclovir; relative risk 0.97, 0.81 to 1.17).[17] Thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome (TTP/HUS) has been reported occasionally in patients with advanced HIV or in bone marrow or renal transplant recipients taking high dose valaciclovir (8 g/day).

What are the precautions?

Older patients and those with renal impairment or taking nephrotoxic drugs—Use caution when prescribing aciclovir and valaciclovir in high doses and closely monitor renal function, as lower doses may be needed owing to increased risk of renal toxicity.

Other possible drug related adverse effects, such as rash, severe headache, and TTP/HUS—Stop antiviral agents.

Drug-drug interactions—No clinically significant interactions have been reported with these agents.

Pregnancy and breast feeding—Management of pregnant women with symptomatic genital herpes should be in consultation with infectious diseases/sexual health and obstetric specialists. Aciclovir is classified as category B (no adequate, well controlled studies of the safety of aciclovir in pregnant women have been reported, and potential benefits should outweigh any risks to the unborn fetus); however, judicious use for treating suspected primary HSV is advocated. Aciclovir has been used in late pregnancy to reduce neonatal transmission. Aciclovir has been detected in breast milk, and caution is advised in using it in mothers who are breast feeding.

How cost effective are they?

Cost effectiveness data for initial and episodic HSV therapy are limited. The antivirals are now available in generic forms, and costs vary globally. Costs may be seen as cost to patient or cost to health services, as some countries dispense antivirals in publicly funded clinics.

How are antivirals taken and monitored?

For genital and labial herpes—Antiviral drugs have comparable efficacy, so the drug choice should be made jointly by the clinician and patient, taking drug cost, dosage convenience, and likely adherence into consideration, as famciclovir and valaciclovir require less frequent dosing than aciclovir. Patients should start oral antivirals within 24-48 hours of symptom onset; topical antivirals have a very limited role. Primary genital herpes may need a longer duration of treatment than recurrent attacks. Monitoring is usually not needed unless patients are at increased risk of nephrotoxicity. Regularly review suppressive therapy (for example, every 6-12 months), allowing discussion with the patient about possible discontinuation.

Disseminated disease, neurological conditions, and neonatal infection—These require intravenous therapy, with good hydration and monitoring of renal function, accompanied by dose reduction if creatinine clearance is reduced. For neonates with HSV encephalitis, prescribe high dose intravenous aciclovir (20 mg/kg/8 h) for a minimum of 21 days; follow-up suppressive treatment with oral valaciclovir is associated with improvement in neurodevelopment outcomes.[11] Adults with HSV encephalitis need a lower dose than neonates (10 mg/kg/8 h) and for 14-21 days.

How do they compare with other options for HSV?

The three current antivirals have comparable efficacy, and no other therapeutic options for genital and labial herpes are available. No commercially available HSV vaccine effectively prevents infection or reduces the severity of symptoms or the frequency of recurrences.[18] Any potential vaccine needs to have efficacy against both HSV-1 and HSV-2, owing to the changing epidemiology of genital herpes.

Newer HSV antivirals including other DNA polymerase inhibitors, such as brincidofovir and valomaciclovir, and a new antiviral class called helicase primase inhibitors (pritelivir and amenamevir, which target the HSV helicase primase complex), are still being evaluated and may have a role in drug resistant HSV infections.[19]

Outcome

The general practitioner diagnoses genital HSV infection clinically and advises oral valaciclovir, as it offers more convenient twice daily dosing and is effective in the treatment of genital herpes with minimal side effects. The patient was also screened for other sexually transmitted infections and given counselling about genital herpes.