Oral Diseases (2006) 12, 254–270. doi: 10.1111/j.1601-0825.2006.01202.x

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REVIEW ARTICLE

Oral and perioral herpes simplex virus type 1 (HSV-1) infection: review of its management*

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Herpes simplex virus type 1 (HSV-1) gives rise to a variety of clinical disorders and is a major cause of morbidity and mortality worldwide. HSV-1 infections are common in oral and perioral area. The aim of the present report was to critically examine the published literature to evaluate the advantages and limitations of therapy of HSV-1 infection in both immunocompetent and immunocompromised patients. Systemic antiviral therapy has been widely accepted as effective for primary herpetic gingivostomatitis. Aciclovir (ACV) 5% cream seems to be the accepted standard topical therapy for herpes labialis, being both effective and well tolerated, although penciclovir 1% cream has been proposed as a potentially useful treatment. Systemic ACV may be effective in reducing the duration of symptoms of recurrent HSV-1 infection, but the optimal timing and dose of the treatment are uncertain. Aciclovir and famciclovir may be of benefit in the acute treatment of severe HSV-1 disease in immunocompromised patients. There is also evidence that prophylactic oral ACV may reduce the frequency and severity of recurrent attack of herpetic infection in immunocompromised patients, but the optimal timing and duration of treatment is uncertain and can vary in different situations.
Oral diseases (2006) **12**, 254–270

Keywords: herpes simplex virus type 1; oral; perioral; antiviral; therapy; drug resistance

Introduction

Herpes simplex virus type 1 (HSV-1) infection occurs worldwide, has no seasonal variation, and only affects humans naturally (Whitley and Roizman, 2001). The prevalence of HSV-1 infection increases gradually from childhood, reaching 70–80% in adulthood (Dakvist *et al*, 1995; Miller *et al*, 1998; Stock *et al*, 2001), and its seroprevalence seems to be greater in lower, than in higher, socioeconomic groups (Corey and Spear, 1986).

Primary HSV-1 infection in oral and perioral sites usually manifests as gingivostomatitis, whereas reactivation of the virus in the trigeminal sensory ganglion gives rise to mild cutaneous and mucocutaneous disease, often termed as recurrent herpes labialis. Recurrent HSV-1 infection in the mouth is less common than herpes labialis and unusual in otherwise healthy persons (Scully, 1989; Lamey and Biagioni, 1996; Holbrook *et al*, 2001).

The present review adds to the current knowledge of oral HSV-1 infection management. A MEDLINE review up to December 2004 was undertaken. The computer search was complemented by a hand search of all bibliographic references. The objective of the report was to analyse critically the literature to evaluate the advantages and limitations of antiviral agents in the treatment of HSV-1 infection for immunocompetent and immunocompromised persons, and examine current issues of HSV-1 antiviral resistance. To our knowledge, there are no recent relevant reviews of the treatment of oral and perioral HSV infections in immunocompetent or immunocompromised persons.

Antiviral agents

In the past, aciclovir (ACV) has been fully evaluated and widely used to treat numerous HSV-related conditions. More recently, newer nucleoside analogues have been investigated as treatment for HSV infections with the aim of building upon the success of ACV.

The antiviral activity and selectivity of the inhibitors of viral DNA synthesis (e.g. ACV, ganciclovir and

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Received 14 June 2005; revised 19 July 2005; accepted 25 July 2005

*Based on a thesis submitted to the postgraduate faculty, Eastman Dental Institute for Oral Health Care Sciences, University of London, in partial fulfilment of the requirements for an MSc degree.

Table 1 Available antiviral drugs for herpetic infection

Drug used	*Route of administration*	*Half-life (h)*	*Oral bioavailability (%)*	*Severe side effects*
Aciclovir	By mouth Topical Intravenously	0.7–1	~15–21	Neuro- and nephro-toxicity
Valaciclovir	By mouth	3–4	~63	Neuro- and nephro-toxicity
Penciclovir	Topical	7–20	~65–77	
Famciclovir	By mouth	2–3	~65–77	Nephrotoxicity
Ganciclovir	By mouth Intravenously	8–10	~1–5	Myelosuppression
Valcangiclovir	By mouth	4–5	~40	Myelosuppression
Foscarnet	Topical Intravenously	2–4	–	Nephrotoxicity
Cidofovir	Topical Intravenously	17–48	–	Nephrotoxicity

related compounds) is based upon their specific activation by herpesvirus-encoded kinases that convert these nucleoside analogues to their monophosphate metabolites (Elion, 1982).

In the first part of this review, we analysed the available antiherpetic drugs (Table 1).

Aciclovir

Aciclovir {9-[(2-hydroxyethoxy)methyl)guanine]} is a nucleoside analogue of guanosine, being transformed by phosphorylation into its active state by viral thymidine kinase (TK). The affinity of ACV for herpesvirus-encoded TK is approximately 200 times greater than for human TK, thus phosphorylation of ACV by the human enzyme occurs at a negligible rate. This selective affinity results in the activation and concentration of ACV in virus-infected cells. Following phosphorylation to ACV monophosphate (aciclo-GMP), normal host cellular enzymes catalyse the sequential phosphorylation to ACV diphosphate (aciclo-GDP) and ACV triphosphate (aciclo-GTP); this nucleoside triphosphate is a potent inhibitor of viral DNA synthesis as it competes with viral nucleotides for incorporation into viral DNA. Once incorporated, it terminates DNA chain synthesis (and thus inhibits viral replication), giving rise to non-functional DNA strands (De Clercq and Walker, 1984; Shinkai and Ohta, 1996). The inhibition of viral DNA synthesis is achieved by a variety of routes: direct inhibition of the viral DNA polymerase by competition with the natural nucleoside triphosphate (dGTP in the case of the triphosphate of ganciclovir and penciclovir as well as ACV), chain termination of the growing viral DNA (ACV) or DNA strand breakage after incorporation of the unnatural nucleotide in the viral DNA (as seen with brivudin triphosphate) (Naesens and De Clercq, 2001).

For many years, ACV has been the mainstay for the treatment and prophylaxis of primary or recurrent infections with HSV or varicella zoster virus (VZV), in either systemic (intravenous or oral) or topical (dermal cream or eye ointment) formulations. Its indications cover the whole range of mucocutaneous, central nervous system or systemic manifestations of HSV and VZV (Cohen *et al*, 1999). The antiviral activity of ACV is, in decreasing order, HSV-1 and -2 > > VZV > EBV > cytomegalovirus (CMV) > human herpes virus-6 (HHV-6), and this is the reason for which ACV therapy of VZV infection requires higher oral doses when compared with HSV infections (Naesens and De Clercq, 2001).

Valaciclovir

Valaciclovir is the L-valine ester prodrug of ACV and has the same mechanism of action, requiring TK-dependent conversion to the monophosphate form. Valaciclovir is absorbed from the gastrointestinal tract and converted to ACV by intestinal and hepatic first-pass metabolism. Sixty-three per cent of the valaciclovir oral dose is absorbed and converted to ACV, compared with the 15–21% absorption of orally administered ACV (Purifoy *et al*, 1993). ACV is detected in plasma as early as 15 min following valaciclovir administration (Shinkai and Ohta, 1996). Thus, valaciclovir acts by increasing the limited oral bioavailability of ACV three- to five-fold (Weller *et al*, 1993; Cassady and Whitley, 1997). Valaciclovir has a safety profile similar to ACV, with mild neurotoxicity and severe nephrotoxicity in animals at single doses of 1 and 2–5 g kg^{-1} respectively. Due to a more convenient dosing regimen (once, twice or three times daily compared with five times daily for ACV), it is likely that valaciclovir will eventually replace ACV in the oral treatment of HSV or VZV infections in immunocompetent persons (Beutner *et al*, 1995). Intravenous ACV is still preferred in severe cases that require hospitalization, such as neonatal herpes, HSV encephalitis or disseminated HSV or VZV infections in immunocompromised persons (Cohen *et al*, 1999).

Penciclovir and famciclovir

The safety profile and antiviral activity spectrum of ACV and penciclovir are largely identical (i.e. active against HSV, VZV and EBV, but less activity against CMV and HHV-6) (Earnshaw *et al*, 1992). However, the drugs differ in terms of cellular uptake, phosphorylation rate, stability of intracellular triphosphate and inhibitory potency for the HSV and VZV DNA polymerase. Although the inhibitory concentrations for HSV or VZV DNA polymerase are 100-fold higher for

penciclovir triphosphate than for ACV triphosphate, this is compensated by the long intracellular half-life of penciclovir triphosphate (7–20 h compared with 0.7–1 h) (Naesens and De Clercq, 2001).

Penciclovir is an acyclic guanine derivative, possessing the same antiviral spectrum as ACV. It undergoes phosphorylation in response to HSV viral TK and is then further phosphorylated by host cell enzymes into a triphosphate which selectively inhibits HSV viral DNA replication (Fife *et al*, 1997; Spruance *et al*, 1997). Penciclovir has approximately one-hundredth the potency of ACV in inhibiting DNA polymerase but, by virtue of its high intracellular concentrations and long half-life, it remains an effective antiviral agent (Vere Hodge and Cheng, 1993; Fife *et al*, 1997). Penciclovir is sensitive to reductions or mutations in TK and is not prescribed for the treatment of alpha herpesviruses resistant to ACV (Cassady and Whitley, 1997).

Famciclovir, the oral prodrug of penciclovir, a diacetate ester derivative of 6-deoxy-penciclovir, has an oral bioavailability three to five times that of ACV. Hydrolysis in the intestinal wall and first-pass metabolism in the liver remove both acetyl moieties. Oxidation of this deacetylated form converts famciclovir to penciclovir (Pue and Benet, 1993). First-pass metabolism results in its rapid conversion to penciclovir, with an oral bioavailability of 77% (Naesens and De Clercq, 2001). Famciclovir has a lower affinity for DNA polymerase than ACV. It is active in prophylaxis against HSV-1 and HSV-2.

Ganciclovir and valganciclovir

Ganciclovir, an ACV analogue, has good activity against HSV-1, HSV-2, CMV and HHV-6, but less so against VZV and EBV. Intravenous ganciclovir is the drug of choice for the treatment or prophylaxis of life-threatening or sight-threatening CMV infection disease in transplant recipients or AIDS patients (Nichols and Boeckh, 2000). The primary mechanism of ganciclovir action against CMV is inhibition of the replication of viral DNA by ganciclovir-5′-triphosphate. This inhibition includes a selective and potent inhibition of the viral DNA polymerase. Ganciclovir is metabolized to the triphosphate form primarily by three cellular enzymes: (i) a deoxyguanosine kinase induced by CMV-infected cells, (ii) guanylate kinase and (iii) phosphoglycerate kinase (Matthews and Boehme, 1988). Due to its low oral bioavailability (6% of ACV), ganciclovir should be administered by daily intravenous infusion. The main side effect of intravenous ganciclovir is myelosuppression, which causes neutropenia or thrombocytopenia.

Valganciclovir is a valyl ester prodrug of ganciclovir, developed for the treatment of CMV retinitis in patients with HIV disease. Oral valganciclovir is rapidly absorbed and hydrolysed to ganciclovir. The oral bioavailability of ganciclovir after oral valganciclovir administration is high. Valganciclovir appears to have a tolerability profile similar to intravenous ganciclovir during induction therapy in patients with AIDS and newly diagnosed CMV retinitis (Curran and Noble, 2001).

Foscarnet and cidofovir

Foscarnet and cidofovir are the only two antiherpes drugs known to inhibit viral DNA synthesis independent of viral TK (or protein kinase). Foscarnet requires no metabolic activation; it inhibits the viral DNA polymerase as a substrate analogue of the pyrophosphate formed during DNA synthesis. Foscarnet inhibits not only all human herpesviruses, but also HIV (Crumpacker, 1992). Intravenous foscarnet is considered second-line therapy for the treatment of CMV in patients who present with severe neutropenia or ganciclovir resistance (Nichols and Boeckh, 2000). Foscarnet is also recommended for severe HSV or VZV infections refractory to ACV (related to TK deficiency) (Cohen *et al*, 1999). Due to its nephrotoxic potential, foscarnet administration requires slow infusion, extensive prehydration and dose adjustment based upon creatinine clearance. No oral formulation of this drug is available. There have been a few reports on the successful use of foscarnet cream in the topical treatment of ACV-resistant HSV lesions (Javaly *et al*, 1999).

Cidofovir, a novel acyclic nucleotide analogue, has been used to treat ACV and foscarnet-resistant HSV, as well as CMV infection (Cassady and Whitley, 1997). Betaherpesviruses are particularly susceptible to the drug. The drug has a mechanism of action similar to other nucleoside analogues (ACV and penciclovir) but employs cellular kinases rather than viral TK to produce the active triphosphate form. Activated cidofovir has higher affinity for viral DNA polymerase and therefore selectively inhibits viral replication (Yang and Datema, 1991). The drug is less potent than ACV *in vitro* but, *in vivo*, it persists in cells for prolonged periods, thus increasing its availability and activity (Lalezari *et al*, 1994). Cidofovir has active metabolites with long half-lives (17–48 h) hence permitting once-weekly dosing. Unfortunately, cidofovir concentrates in renal tissue 100 times more than in other tissues and can give rise to severe proximal convoluted tubule nephrotoxicity (Yang and Datema, 1991).

Management of primary herpetic gingivostomatitis

Although herpetic gingivostomatitis is a self-limiting disease, affected individuals may experience severe pain and be unable to eat or drink. To date, not many studies have demonstrated definitively that antiviral drugs are effective for the treatment of primary herpetic gingivostomatitis (Table 2).

Evidence from three randomized controlled trials (RCTs) (Ducoulombier *et al*, 1988; Aoki *et al*, 1993; Amir *et al*, 1997) suggested that ACV suspension may be effective in reducing the duration of symptoms of herpetic gingivostomatitis in young children, but the optimal timing and the dose of antiviral therapy are uncertain. For instance, its beneficial effect *vs* placebo was evident in all clinical variables evaluated in one study (Amir *et al*, 1997). No child in the ACV group required hospitalization compared with three children in the placebo group who were admitted for

Table 2 Available studies for the treatment of primary HSV-1 infections (*in vivo*)

References	*Type of study*	*C*[a]	*Total study population*	*Drug used*	*Findings*
Sullender *et al* (1987)	Population analysis[b]	III	18	Aciclovir 600 or 300 mg m^{-2}	Drug well tolerated by young children; no adverse effects noted
Mueller and Weigand (1988)	Open study, non-blind, non-controlled	III	37	Aciclovir 100–200 mg 5 times daily for 5 days	Fever disappeared after the third day of treatment, with improvement in the oral lesions
Ducoulombier *et al* (1988)	Randomized double-blind placebo-controlled	I	18	Aciclovir 200 mg 5 times daily for 5 days	Less pain and hypersalivation in the aciclovir group
Aoki *et al* (1993)	Randomized double-blind placebo-controlled	I	68	Aciclovir 600 mg m^{-2} q.i.d. for 10 days	In the aciclovir group, shorter times for disappearance of the lesions or completion of viral shedding
Cataldo *et al* (1993)	Retrospective study	II	162	Aciclovir 200 mg 5 times daily for 5–6 days	Prognosis more favourable, because of fast regression of the symptoms
Amir *et al* (1997)	Randomized double-blind placebo-controlled	I	61	Aciclovir 15 mg kg^{-1} five times daily for 7 days	If started in the first 3 days of onset, shortens clinical signs and infectivity
Tod *et al* (2001)	Population analysis[b]	II	79	Aciclovir 24 mg kg^{-1} t.i.d. or q.i.d.	Adequate regimen. It has to be taken t.i.d. for patients younger than 1 month of age or q.i.d. otherwise

[a]Evidence classification scheme for a therapeutic intervention (Brainin *et al*, 2004).
[b]Pharmacokinetics of oral aciclovir in infants and children.

rehydration; after 3 days of treatment all viral cultures became negative, compared with almost 50% remaining positive at day 6 in the placebo group. Concern has been expressed over the possibility of selection of resistant strains once ACV is used for such common disorders, but a 7-day treatment in normal children is unlikely to create any problem; in fact, it has been used to prevent recurrent genital herpes for more than 6 years, and no resistant strains have been isolated (Amir *et al*, 1997).

The efficacy of ACV suspension has been also reported in an open study (Mueller and Weigand, 1988) and in one clinical and epidemiological study (Cataldo *et al*, 1993).

Aciclovir is approved for the treatment of HSV and VZV infections in children by the intravenous and oral routes, but its use by the oral route in children younger than 2 years of age is limited due to a lack of pharmacokinetic data. However, two studies suggested that their proposed dosing regimen is well tolerated by young children (Sullender *et al*, 1987; Tod *et al*, 2001).

It has been suggested that valaciclovir and famciclovir may be effective in the treatment of acute herpetic gingivostomatitis. Valaciclovir is prescribed in doses of 1 g three times daily for 7 days for herpes zoster, although 1 g twice daily should be effective for primary herpetic gingivostomatitis. The recommended dosage of famciclovir for treatment of herpes acute herpetic gingivostomatitis is 500 mg twice daily (Chauvin and Ajar, 2002).

Management of recurrent HSV-1 infection

The selection of an appropriate antiviral compound and drug delivery format (intravenous, oral or topical) for herpes simplex labialis infections in immunocompetent individuals can present a dilemma for many practitioners. Numerous agents are available, most of which focus upon the treatment of painful symptoms.

Topical treatment of herpes labialis

Aciclovir (5%) cream seems to be the accepted standard therapy for herpes labialis, being both effective and well tolerated. Its availability as a generic preparation further has improved the benefit-to-cost ratio (Spruance *et al*, 1995; Raborn *et al*, 1997; Leflore *et al*, 2000; Esmann, 2001) (Table 3).

Topical ACV has low local bioavailability and it penetrates poorly the tissues (Freeman *et al*, 1986; Raborn *et al*, 1989, 1997), indeed the evidence of its efficacy is perhaps equivocal. ACV was shown to penetrate the skin more effectively in cream, rather than in ointment, formulation (Freeman *et al*, 1986).

Studies of ACV in immunocompetent individuals have provided evidence of its efficacy for herpes labialis. To date, four RCTs analysed the use of ACV cream *vs* placebo for the topical treatment of recurrent HSV-1 infection. Episodes of herpes labialis treated with ACV had significantly showed a good response if applied before the onset of vesicles (Fiddian *et al*, 1983; Spruance *et al*, 2001). The duration of vesiculation and local itching was reduced with ACV 5% cream containing propylene glycol (Van Vloten *et al*, 1983); the authors also suggested that the penetration through the skin, as well as the timing of initiation of therapy, was a limiting factor to efficacy. The efficacy of 5% ACV in a modified aqueous cream vehicle (ACV-MAC) is no better than conventional cream (Raborn *et al*, 1989). A recent RCT demonstrated that 5% ACV with 1% hydrocortisone (ME-609) reduced healing time, lesion size and pain of herpes labialis (Evans *et al*, 2002). A double-blind study demonstrated that tromantadine hydrochloride (Viru-Merz Serol, CAS 53783-83-8) is as effective as ACV (Diezel *et al*, 1993).

Randomized controlled trials have demonstrated that 1% penciclovir cream decreases pain, promoting early cessation of viral shedding (Spruance *et al*, 1997; Raborn *et al*, 2002) and reduces maximum lesion size

Table 3 Available studies for the topical treatment of recurrent HSV-1 infections

References	*Type of study*	*C*	*Total study population*[a]	*Drug used*	*Findings*
Fiddian *et al* (1983)	Double blind placebo-controlled trial	II	49	Aciclovir 5% cream applied for 5 days	Shorter times to formation of ulcer or crust and to complete healing
Van Vloten *et al* (1983)	Randomized double-blind placebo-controlled	I	30	Aciclovir 5% cream, containing propylene glycol	Reduction in the duration of signs and in the total healing time
Raborn *et al* (1989)	Randomized double-blind placebo-controlled	I	59	Aciclovir 5% cream in an aqueous cream vehicle	No differences for lesion or healing
Femiano *et al* (2001)	Open study	II	40	Aciclovir 5% cream *vs* penciclovir 1% cream	Penciclovir was superior; it has to be applied every 2 h for 4 days
Spruance *et al* (2001)	Randomized double-blind placebo-controlled	I	1385	Aciclovir 5% cream	Fewer symptoms, if applied every 3 h for 4 days
Evans *et al* (2002)	Randomized double-blind placebo-controlled (UVR-induced)	I	380	Aciclovir 5% cream + 1% hydrocortisone. Applied six times daily for 5 days	Reduced incidence, healing time, lesion size, and lesion tenderness
Lawee *et al* 1988)	Randomized double-blind placebo-controlled	I	143	Foscarnet 3% cream	Beneficial effect of foscarnet limited, if started in the prevesicular stage
Bernstein *et al* (1997)	Randomized double-blind placebo-controlled (UVR-induced)	I	302	Foscarnet 3% cream or vehicle cream	It can reduce the mean lesion area, and the healing time
Spruance *et al* (1997)	Randomized double-blind placebo-controlled	I	1573	Penciclovir 1% cream. Applied every 2 h for 4 days	Less symptoms and virus shedding
Lin *et al* (2002)	Randomized double-blind aciclovir-controlled	I	225	Penciclovir 1% cream *vs* aciclovir 3% cream	Penciclovir is better. It has to be applied every 3 h for 4 days
Boon *et al* (2000)	Randomized double-blind placebo-controlled	I	541	Penciclovir 1% cream	Reduced lesion area, symptoms; to be applied every 2 h for 4 days
Raborn *et al* (2002)	Randomized double-blind placebo-controlled	I	3057	Penciclovir 1% cream	Penciclovir cream outperformed the placebo
Anonymous (1996)	Randomized double-blind placebo-controlled	I	846	N-docosanol 10% cream	Doconosal failed to show efficacy *vs* placebo
Sacks *et al* (2001)	Randomized double-blind placebo-controlled	I	743	N-docosanol 10% cream	Can reduce symptoms. It has to be applied 5 times daily until healing
Spruance *et al*. (1990a)	Randomized double-blind placebo-controlled	I	301	Idoxuridine 15% in dimethyl sulphoxide	Can reduce symptoms. It has to be applied every 3 h for 4 days
Diezel *et al* (1993)	Randomized double-blind	I	198	Tromantadine hydrochloride *vs* aciclovir	Rapid healing was achieved with both medications

[a]Studies evaluating antiviral therapy of naturally recurrent herpes labialis in immunocompetent patients.

(Boon *et al*, 2000) when compared with placebo. Moreover, the result of an open study demonstrated the inefficacy of ACV for the treatment of herpes labialis, confirming besides that penciclovir is effective and superior to ACV (Femiano *et al*, 2001). A shorter time to resolution of all symptoms was also reported for penciclovir 1% cream compared with ACV 3% cream by one RCT (Lin *et al*, 2002).

Unlike ACV, late application of penciclovir can still produce clinical benefit (Fife *et al*, 1997); however, penciclovir should be applied every 2 h (Spruance *et al*, 1997; Raborn *et al*, 2002) whereas ACV should be applied every 4 h (Spruance *et al*, 2001).

Randomized controlled trials of topical foscarnet 3% cream, applied four times daily, *vs* placebo have demonstrated that it can reduce the duration of virus shedding, development of vesicles and duration of ulcers (Lawee *et al*, 1988; Bernstein *et al*, 1997).

An over-the-counter treatment for recurrent herpetic infection (Anonymous, 1996; Pope *et al*, 1998; Sacks *et al*, 2001), 10% n-docosanol cream is not so effective. Likewise, topical 15% idoxuridine (IDU) in dimethyl sulphoxide (DMSO) is not of relevant clinical benefit (Spruance *et al*, 1990a).

Systemic therapy of herpes labialis

Systemic therapy of herpes labialis has been investigated when it became apparent that topical treatment might be limited by poor penetration (Table 4).

Results of RCTs suggest that systemic ACV may be effective in reducing the duration of symptoms of recurrent HSV-1 infection, but the optimal timing and the dose of the treatment are uncertain. It certainly has a significant antiviral action, but cannot alter either the time to complete healing or duration of pain (Raborn *et al*, 1987; Spruance *et al*, 1990b).

Because of the rapid development of the vesicle stage (<12 h) and the fast decrease in detectable virus after 48 h, studies of antiviral therapy empirically necessitate early treatment within the first several hours of signs and symptoms or a recurrence. The BMJ Clinical Evidence Guidelines reiterated that no trials compare early *vs* late treatment, so no definite conclusion about the efficacy of delayed treatment can be drawn (Clin Evid [online], 2003).

Results of two RCTs suggested that systemic famciclovir has marginal clinical benefit in the treatment of herpes labialis (Spruance *et al*, 1999; Spruance and McKeough, 2000).

Table 4 Available studies for the systemic treatment of recurrent HSV-1 infections

References	*Type of study*	*C*	*Total study population*[a]	*Drug used*	*Findings*
Raborn *et al* (1987)	Randomized double-blind placebo-controlled	I	149	Aciclovir 200 mg five times daily for 5 days	Aciclovir showed an antiviral effect. It has to be taken five times daily for 5 days
Spruance *et al* (1990b)	Randomized double-blind placebo-controlled	I	174	Aciclovir 400 mg five times daily for 5 days	Reduced signs and symptoms. It has to be taken five times daily for 5 days
Spruance *et al* (1991)	Randomized double-blind placebo-controlled (UVR-induced)	I	15	Aciclovir 200 mg five times daily for 5 days	ACV therapy can be efficacious, but some rapidly developing lesions are unresponsive
Spruance *et al* (1999)	Randomized double-blind placebo-controlled (UVR-induced)	I	102	Famciclovir 125–250–500 mg .i.d. for 5 days	It has to be taken five times daily for 5 days. Evaluation of higher drug dose is warranted
Spruance and McKeough (2000)	Randomized double-blind controlled (UVR-induced)	I	29	Famciclovir 500 mg t.i.d. + topical fluocinonide 0.05% *vs* famciclovir 500 mg t.i.d. + topical vehicle	Corticosteroids in combination with an antiviral agent may be safe and beneficial for episodic treatment of herpes labialis
Spruance *et al* (2002)	Randomized double-blind placebo-controlled	I	1856	Valaciclovir 2 g b.i.d. for 1 day or valaciclovir 2 g b.i.d. for 1 day + 1 g b.i.d. for the 2nd	Reduced symptoms. More aborted lesions. Similar data for both formulations
Laiskonis *et al* (2002)	Randomized double-blind controlled	I	308	Valaciclovir 1 g b.i.d. for 1 day *vs* valaciclovir 0.5 g b.i.d. for 3 days	No differences between the two groups. Pain resolved rapidly
Chosidow *et al* (2003)	Randomized clinical trial	I	249	Single course of valaciclovir (0.5, 1 and 2 g)	No differences between the three groups in rates of aborted lesions at day 3

[a]Studies evaluating antiviral therapy of naturally recurrent herpes labialis in immunocompetent patients.

To date, there is evidence of the efficacy of systemic valaciclovir for the treatment of herpes labialis (Laiskonis *et al*, 2002; Spruance *et al*, 2002; Chosidow *et al*, 2003). Therapy started during the prodromal phase of the disease seems to be of clinical benefit; however, there is no evidence on the correct dose.

As reported in another recent review (Jensen *et al*, 2004), no studies directly compared different antivirals.

Treatment for immunocompromised patients

In immunocompromised patients, recurrent HSV-1 infection may be 'atypical', usually more extensive and aggressive than that of immunocompetent individuals, slow healing and extremely painful (Cohen and Greenberg, 1985; Epstein *et al*, 1990; Woo *et al*, 1990) (Table 5). Prior to the availability of effective anti-viral therapies, recurrent severe HSV-1 infection was a major cause of morbidity and mortality in immunocompromised patients (Oakley *et al*, 1997; Scott *et al*, 1997).

Patients most liable to clinically significant HSV-1 recurrent infection include those receiving chemotherapy prior to bone marrow transplantation (Barrett, 1986; Epstein *et al*, 1990; Schubert *et al*, 1990;

Table 5 Studies for evaluating topical or systemic treatment of oral and perioral HSV-1 infection in immunocompromised patients

References	*Type of study*	*C*	*Total study population*	*Drug used*	*Findings*
Selby *et al* (1979)	Open study	III	23	Parenteral aciclovir	It seemed to arrest safely the progress of the infections; most effective if given early
Meyers *et al* (1982)	Randomized double-blind placebo-controlled	I	97	Intravenous aciclovir	Safe and effective for immunocompromised patients
Whitley *et al* (1984)	Double-blind placebo-controlled	II	63	Topical aciclovir	Aciclovir therapy was of clinical benefit. No adverse reactions
Shepp *et al* (1985)	Randomized double-blind placebo-controlled	I	21	Aciclovir 400 mg five times daily for 10 days	Reduced duration of viral shedding, new lesion formation, and resolution of pain
Romanowski *et al* (2000)	Randomized controlled double-blind parallel-group	I	293	Famciclovir 500 mg b.i.d. *vs* aciclovir 400 mg five times daily	7 days' treatment of famciclovir is effective and well tolerated as high-dose aciclovir for infections in HIV-infected individuals
Safrin *et al* (1991)	Randomized controlled	II	14	Foscarnet 40 mg kg^{-1} i.v. every 8 h *vs* vidarabine 15 mg kg^{-1} i.v. per day for 10–42 days	For the treatment of ACV-resistant infection in patients with AIDS; foscarnet has superior efficacy and less frequent serious toxicity than vidarabine. High frequency of relapse
Javaly *et al* (1999)	Phase I/II open-label non-randomized multicenter trial	II	20	Foscarnet 1% cream five times a day for a mean of 34.5 days	This drug could be a safe and effective treatment for ACV-unresponsive infection in AIDS patients
Lalezari *et al* (1994)	Randomized double-blind placebo-controlled	I	30	Cidofovir (0.3% or 1%) cream once daily for 5 days	Cidofovir provided significant benefits in healing, virological effect, pain reduction

Bergmann *et al*, 1995; Warkentin *et al*, 2002; Eisen *et al*, 2003) and those receiving immunosuppressive therapy for preventing rejection after allograft transplant (Rand *et al*, 1977; Pollard *et al*, 1982; Greenberg *et al*, 1987). Oral and perioral HSV infection is common in patients with HIV disease (Mann *et al*, 1984; Silverman *et al*, 1986; Phelan *et al*, 1987; MacPhail *et al*, 1989). Although the exact frequency and severity of recurrent HSV-1 infection in HIV disease remain controversial, HSV-1 seropositivity is the principal indicator of potential risk of recurrent HSV-1 infection in such liable patients (Esmann, 2001) and thus mirrors pathways with other acquired immunodeficiencies.

Moreover, some groups of immunocompromised patients can develop severe herpetic infection refractory to usual antiviral drug therapy. Typically, such patients are treated with a standard oral ACV therapy at a dose of 200 mg, five times a day for the first 3–5 days, after obtaining a culture of the lesions to verify HSV aetiology. If the response is poor, the dose may be increased to 800 mg five times a day. If there is no notable clinical benefit after 5–7 days, it is unlikely that the lesion will respond to intravenous ACV (or chemically and structurally related drugs such as valacyclovir (VCV) or famciclovir), thus an alternative regimen should be assigned. Aciclovir susceptibility studies of viral isolated should be undertaken. Mucocutaneous lesions may benefit from topical treatment. If the lesion is inaccessible, therapy with intravenous foscarnet (e.g. 40 mg kg^{-1} three times daily or 60 mg kg^{-1} twice daily), for 10 days or until complete resolution of the lesions may be of benefit. If foscarnet fails to be effective, intravenous cidofovir (or application of compounded 1–3% topical cidofovir ointment) may be considered. Vidarabine is reserved for situations in which all these therapies fail. If lesions recur, high-dose oral ACV (800 mg, five times daily) or intravenous foscarnet (40 mg kg^{-1} t.i.d. or 60 mg kg^{-1} twice daily) should be initiated. When lesions occur in a different location, the patient should be treated initially with standard doses of oral ACV (200 mg, five times daily) and the above protocol should be followed should there be clinical failure (Chilukuri and Rosen, 2003).

Aciclovir is the drug of choice for herpetic infection in immunocompromised patients, but evidence of its clinical efficacy is scarce. Intravenous ACV is effective in preventing HSV reactivation but expensive, whereas oral formulation is also effective and less expensive but, due to its low bioavailability, patients need to receive high doses (Dignani *et al*, 2002). RCTs demonstrated that systemic ACV has a variable effect in the treatment of herpetic infection in immunocompromised patients (Meyers *et al*, 1982; Whitley *et al*, 1984; Shepp *et al*, 1985) and another open study reported its efficacy if given early (Selby *et al*, 1979).

The efficacy of oral ACV and oral famciclovir has also been reported (Romanowski *et al*, 2000) in HIV-infected individuals with recurrent HSV infection (orolabial or genital). Similar to ACV, famciclovir is equally effective in preventing new lesion formation, but it has the convenience of less frequent dosing.

Intravenous foscarnet is more effective, and better tolerated, than vidarabine for the treatment of mucocutaneous herpetic lesions in patients with HIV disease (Safrin *et al*, 1991).

Foscarnet 1% cream (Javaly *et al*, 1999) and cidofovir gel (Lalezari *et al*, 1994) have been reported to be safe and effective for the treatment of mucocutaneous herpetic lesions, clinically unresponsive to systemic ACV treatment, in patients with HIV disease.

Prophylactic therapy of recurrent oral and perioral HSV-1 infection

Topical therapy and sunscreen

Topical ACV or foscarnet creams are not effective prophylaxis for UV-induced herpes labialis (Bernstein *et al*, 1997; Evans *et al*, 2002) (Table 6). Only Raborn *et al* (1997) demonstrated that prophylactic ACV cream reduced the frequency of herpes labialis in skiers, but this study was flawed by the potential sun-blocking activity of the drug. Two small crossover RCTs found that sunscreens reduce the rate of recurrence of herpes labialis due to sunlight (Rooney *et al*, 1991; Duteil *et al*, 1998).

Antiviral agents for immunocompetent patients

Selected immunocompetent patients for prophylactic therapy or recurrent oral HSV infection have been described in Table 7.

The results of one RCT suggest that prophylactic oral ACV may reduce the frequency and severity of recurrent attack of herpetic infection in immunocompetent patients, but the optimal timing and duration of treatment is uncertain (Rooney *et al*, 1993). The effectiveness of prophylactic oral ACV was also proved in two open studies of persons with a history of sun-induced recurrences (Spruance *et al*, 1988; Shelley and Shelley, 1996). However, other RCTs did not indicate systemic ACV to be of some benefit to prevent sun-induced herpes labialis compared with placebo (Raborn *et al*, 1998).

Valaciclovir may be effective and well tolerated for the prevention of recurrent herpes labialis in otherwise well persons (Baker *et al*, 2000; Baker and Eisen, 2003). It may also be of benefit for oral prophylaxis for facial dermal abrasion in susceptible patients (Gilbert, 2001). A recent RCT reported that HSV recrudescence after routine dental treatment is suppressed by a short course of valaciclovir (2 g b.i.d. for 1 day and 1 g b.i.d. for another day) (Miller *et al*, 2004).

Famciclovir may also be useful as prophylactic anti-HSV therapy for cutaneous laser resurfacing (Alster and Nanni, 1999) in patients with a strong history of HSV. Recurrent herpes-associated erythema multiforme may be controlled by continuous treatment with low-dose oral ACV (Lemak *et al*, 1986; Morel and Barth, 1986; Molin, 1987; Huff, 1988; Tatnall *et al*, 1995; Cheriyan and Patterson, 1996; Molnar and Matulis, 2002), also in children (Weston and Morelli, 1997). One RCT of continuous ACV therapy in recurrent erythema multiforme (Tatnall *et al*, 1995) demonstrated that 400 mg

Table 6 Studies for evaluating antiviral prophylaxis of HSV-1 infection

References	*Type of study*	*C*	*Total study population*	*Drug used*	*Findings*
Saral *et al* (1981)	Double-blind placebo-controlled	II	20	Aciclovir or placebo was administered for 18 days, starting 3 days before transplant	Culture-positive HSV lesions developed during the study only in 70% of patients who received placebo. No evidence of drug toxicity
Gluckman *et al* (1983)	Double-blind placebo-controlled	II	39	Aciclovir 200 mg every 6 h from 8 days before to 35 days after BMT	The protection against HSV infection was complete in the treated group even in patients with high antibody titres before transplantation
Hann *et al* (1983)	Randomized double-blind placebo-controlled	I	59	Aciclovir i.v. 5 mg kg^{-1} during neutropenia	Aciclovir can provide effective prophylaxis in i mmunocompromised patients given BMT
Prentice (1983)	Placebo-controlled	II	79	Aciclovir i.v. 5 mg kg^{-1} b.i.d. during neutropenia	Aciclovir provided good protection against HSV infection in BMT patients
Wade *et al* (1984)	Double-blind placebo-controlled	II	49	Oral aciclovir for 5 weeks beginning 1 week before transplant	Less patients in the aciclovir group developed HSV infection
Anderson *et al* (1984)	Double-blind placebo-controlled	II	41	Aciclovir 200 mg q.i.d. for 6 weeks	Oral aciclovir reduced the incidence of clinical HSV infection and the incidence of viral isolates
Shepp *et al* (1985)	Randomized double-blind placebo-controlled	I	27	Aciclovir i.v. 250 mg m^{-2} once daily for 4 weeks	Aciclovir can delay time to appearance of culture -positive HSV lesions after BMT
Seale *et al* (1985)	Randomized double-blind placebo-controlled	I	40	Aciclovir for 30 days	HSV infections in immunosuppressed renal allograft recipients can be prevented and deferred with oral therapy
Griffin *et al* (1985)	Double-blind placebo-controlled	II	81	Aciclovir	After renal transplant, the group treated had significantly fewer clinical infections and viral shedding
Pettersson *et al* (1985)	Double-blind placebo-controlled	II	35	Aciclovir 200 mg q.i.d. for 28 days	None allocated to aciclovir showed any signs of infection
Spruance *et al* (1988)	Parallel-group short-term placebo-controlled	I	147	Aciclovir 400 mg b.i.d. for 7 days during ski vacation	Significantly fewer individuals receiving aciclovir developed l esions than placebo recipient
Rooney *et al* (1993)	Randomized double-blind placebo-controlled	I	22	Aciclovir 400 mg b.i.d. for 4 months	Treatment resulted in a reduction in the number of clinical and virus recurrences
Bergmann *et al* (1995)	Randomized double-blind placebo-controlled	I	74	Aciclovir 800 mg daily for 28 days	Prophylaxis should be done for patients with AML during remission induction therapy
Shelley and Shelley (1996)	Open study	II	32	Aciclovir 800 mg single dose	This dosage is a cost -effective alternative to long-term dosing

Table 6 (*Continued*)

References	*Type of study*	*C*	*Total study population*	*Drug used*	*Findings*
Bergmann *et al* (1997)	Randomized double-blind placebo-controlled	I	90	Aciclovir 800 mg daily for 28 days	Aciclovir has an impact only on fever in AML patients
Raborn *et al* (1997)	Randomized double-blind placebo-controlled	I	181	Aciclovir 5% cream	The aciclovir group was significantly better during the follow-up period
Raborn *et al* (1998)	Randomized double-blind placebo-controlled	I	237	Aciclovir 800 mg b.i.d. for 3–7 days	Oral aciclovir was not significantly better than a placebo
Schacker *et al* (1998)	Randomized double-blind placebo-controlled	I	48	Famciclovir 500 mg b.i.d. for 8 weeks	Famciclovir results in significant reductions in the symptoms, and shedding of HSV among HIV-positive persons
Alster and Nanni (1999)	Open controlled	II	99	Famciclovir 250 mg b.i.d. *vs* famciclovir 500 mg b.i.d.	Beginning 1 day prior to laser resurfacing and continuing for 10 days. No HSV recurrences were seen in 90% of patients' treatment at either dose
Baker *et al* (2000)	Long-term parallel group placebo-controlled	II	40	Valaciclovir 500 mg once daily for 4 months	This dosage showed 53% of reduction in the frequency of recurrences compared with placebo
Dignani *et al* (2002)	Open study placebo-controlled	II	189	i.v. aciclovir 5 mg kg^{-1} t.i.d. *vs* valaciclovir 400 mg b.i.d.	HSV reactivations were seen in 2.7%, 2% and 45% of autologous progenitor cell transplantation patients in the valacyclovir, ACV, and no-prophylaxis groups respectively
Warkentin *et al* (2002)	Randomized controlled	I	151	Aciclovir 400 mg t.i.d. *vs* valaciclovir 500 mg b.i.d. or valaciclovir 250 mg b.i.d.	Prophylactic treatment with valaciclovir is an effective and safe alternative to ACV for preventing reactivation in patients with haematological malignancies
Eisen *et al* (2003)	Open study	II	120	Aciclovir 600 mg q.i.d. *vs* valaciclovir 500 mg b.i.d.	Both drugs are helpful for preventing HSV infection in BMT patients
Baker and Eisen (2003)	Randomized double-blind placebo-controlled	I	98	Valaciclovir 500 mg once daily for 16 weeks	60% in the valaciclovir group and 38% in the placebo group were recurrence-free
Orlowski *et al* (2004)	Randomized controlled	I	81	Valaciclovir 0,5 g or 1 g t.i.d.	Valaciclovir at either of the two doses is safe and provides effective action
Miller *et al* (2004)	Randomized double-blind placebo-controlled	I	125	Valaciclovir 2 g or 1 g b.i.d.	HSV recrudescence after outine dental treatment is suppressed by valaciclovir prophylaxis

twice daily completely suppresses recurrent attacks and, in some cases, may induce disease remission. It has also been reported that EM unresponsive to prophylactic oral ACV may be successfully treated with prophylactic valaciclovir (Kerob *et al*, 1998).

Antiviral agents for immunocompromised patients

Aciclovir is often needed as prophylactic therapy in HSV-seropositive patients with acute leukaemia undergoing either remission induction therapy or bone marrow transplantation for reducing or preventing herpes labialis and herpes simplex virus culture-positive intraoral ulcers (Saral *et al*, 1981; Gluckman *et al*, 1983; Hann *et al*, 1983; Barrett, 1986; Montgomey *et al*, 1986; Greenberg *et al*, 1987; Redding and Montgomery, 1989).

A review of relevant RCTs indicates that prophylactic use of ACV reduces the frequency and severity of

Table 7 Selected immunocompetent patients for prophylactic therapy for herpes labialis (Gilbert, 2001)

Patients with frequent recurrent episodes (≥6 episodes year^{-1})
History of herpes associated erythema multiforme
Susceptible patients anticipating a period of intense sun exposure or stress
Susceptible patients undergoing surgical procedures on the trigeminal ganglion
Susceptible patients undergoing peri- or intra-oral surgery
Immunocompetent patients
Patients with herpes gladiatorum
Selected healthcare professionals to lower the potential for virus transmission
Selected people in the advertising, television and entertainment industries

attacks against reactivated HSV-1 infections in severely immunocompromised patients (Hann *et al*, 1983; Wade *et al*, 1984). The good efficacy of ACV, as prophylaxis of herpetic infection *vs* placebo, in immunocompromised patients, undergoing bone-marrow transplantation or chemotherapy, has been evaluated also by non-randomized trials (Saral *et al*, 1981; Gluckman *et al*, 1983; Anderson *et al*, 1984). Both oral and intravenous ACV provide effective prophylaxis against reactivation of HSV-1 (Prentice, 1983; Shepp *et al*, 1985; Bergmann *et al*, 1995, 1997).

Oral ACV may also provide effective and safe prophylaxis for post-renal transplant HSV-1 infection (Pettersson *et al*, 1985; Seale *et al*, 1985).

The good efficacy and safety of both oral valaciclovir and oral ACV has been demonstrated (Warkentin *et al*, 2002; Eisen *et al*, 2003) for patients with haematological malignancies requiring chemotherapy or stem cell transplantation. Moreover, oral valaciclovir was as effective as intravenous ACV for the prophylaxis of HSV reactivation in autologous progenitor cell transplantation patients (Dignani *et al*, 2002), and also more effective in patients undergoing dose-intensive remission induction or consolidation chemotherapy of acute leukaemia (Orlowski *et al*, 2004).

Famciclovir resulted in clinically and statistically significant reductions in the symptoms associated with HSV infection, and the symptomatic and asymptomatic shedding of HSV in HIV-positive persons in one RCT (Schacker *et al*, 1998).

Resistance to antiherpes drugs

Since ACV became available for clinical application, it has been used primarily in the prevention and treatment of HSV infections. ACV-resistant HSV strains have been observed *in vivo* since the beginning (Burns *et al*, 1982; Crumpacker *et al*, 1982; Sibrack *et al*, 1982). These resistant strains can be detected *in vitro* by phenotypic tests which determine the antiviral concentration-inhibiting viral replication by 50%. Several other methods have been used to determine the sensitivity of the HSV strains to ACV, including determining the cytopathic effect of the virus (using the plaque reduction assay and colorimetric techniques), and the detection of DNA replication (by hybridization or antigen production by flow cytometry) (Langlois *et al*, 1986; Swierkosz *et al*, 1987; Danve-Szatanek *et al*, 2003).

Herpes simplex virus type 1 infection in immunocompetent patients usually requires short-term antiviral therapy, thus HSV drug resistance is unlikely to arise (Gilbert *et al*, 2002). In contrast, immunocompromised patients often require recurrent and long-term antiviral therapy, and thus are liable to develop drug-resistant strains of HSV (Erlich *et al*, 1989; Englund *et al*, 1990; Christophers *et al*, 1998; Chen *et al*, 2000; Morfin *et al*, 2000; Chilukuri and Rosen, 2003).

The resistance of HSV to ACV is due to one or more of the following mechanisms: (i) complete deficiency in viral TK activity (TK-deficient virus), (ii) decreased production of viral TK (TK low producer virus), (iii) viral TK protein with altered substrate specificity (TK-altered virus; the enzyme is able to phosphorylate thymidine not ACV), or (iv) a viral DNA polymerase with altered substrate specificity (DNA pol altered) (Larder *et al*, 1983; Gilbert *et al*, 2002; Chibo *et al*, 2004). Alteration or absence of the TK protein, hence preventing ACV phosphorylation (Erlich *et al*, 1989; Whitley and Roizman, 2001), is the most frequently reported mechanism, probably because TK is not essential for viral replication in most tissues and cultured cells (Gaudreau *et al*, 1998). A TK-deficient phenotype (Hill *et al*, 1991) has been observed in 95% of ACV-resistant isolates. However, several reports have demonstrated that at least some TK activity is needed for HSV reactivation from latency in neural ganglia (Coen *et al*, 1989; Tenser *et al*, 1989; Wilcox *et al*, 1992).

Deficiency in TK may render the virus cross-resistant to other nucleoside analogues that are dependent upon TK for phosphorylation to the active form (e.g. penciclovir and ganciclovir). Occasionally, HSV strains are TK altered and maintain the ability to phosphorylate the natural substrate, thymidine, but selectively lose the ability to phosphorylate ACV. Others retain only a fraction of normal TK activity (1–15%) but are considered ACV resistant in susceptibility assays (Hill *et al*, 1991).

A mutation of the viral DNA polymerase gene results in the failure to incorporate ACV triphosphate in progeny DNA molecules (Sacks *et al*, 1989), but this is much less likely to account for ACV resistance than defect of TK. Antiviral drugs with a non-TK-dependent mode of action have been used since the emergence of ACV-resistant strains (Safrin *et al*, 1994; Naik *et al*, 1995), however foscarnet-resistant strains have appeared (Safrin *et al*, 1994; Darville *et al*, 1998; Chen *et al*, 2000). Resistance to foscarnet is explained by the presence of a mutation in the DNA polymerase gene (Gibbs *et al*, 1988).

Most of the ACV-resistant HSV isolates are also resistant to penciclovir, the mechanism of resistance of these strains being either an altered TK (Boyd *et al*, 1993) or a mutation in viral DNA polymerase (Chiou *et al*, 1995). Foscarnet and cidofovir act directly on viral DNA and both these molecules can be active on viruses

resistant to ACV because of a mutation in the TK gene (Safrin *et al*, 1991; Blot *et al*, 2000). However, in clinical practice, they may be associated with a significant level of toxicity (Morfin and Thouvenot, 2003). Another means of managing ACV-resistant HSV infection is to improve the immune status of the patient, when possible, by decreasing immunosuppressive treatments (Collins and Oliver, 1986).

To date, there has been no extensive survey of the rate of emergence of drug-resistant HSV isolates according to the duration of antiviral therapy (Gilbert *et al*, 2002).

Previous surveys among immunocompetent patients have shown a prevalence of ACV resistance varying between 0% and 0.6%, whereas among immunocompromised patients, the rates of detection of ACV-resistant HSV isolates varied from 3% to 6% (Englund *et al*, 1990; Nugier *et al*, 1992; Christophers *et al*, 1998). More recently, a prevalence of resistance to ACV of 0.3% (Danve-Szatanek *et al*, 2003) and 0.11% (Boon *et al*, 2000) in immunocompetent patients and of 3.6% for immunocompromised individuals (Danve-Szatanek *et al*, 2003) was reported.

In almost all instances, among immunocompetent patients, resistance to ACV is cleared normally with no adverse clinical outcome (Bacon *et al*, 2003; Morfin and Thouvenot, 2003). Most ACV-resistant HSV isolates of immunocompetent individuals have been of genital origins (Straus *et al*, 1984; Fife *et al*, 1994).

Among immunocompromised patients, the increase in the use of ACV is linked to the growth in the number and survival of patients among whom it is used for prophylactic or curative treatment. Furthermore, the development of new antiviral molecules derived from ACV (TK dependent), such as valaciclovir, penciclovir and ganciclovir, increases the risk of selection pressure of resistant strains (Danve-Szatanek *et al*, 2003).

The prevalence of resistance to ACV is very strongly linked to the type of immunosuppression, and when serious immunosuppression is combined with lengthy exposure to ACV, the risk of appearance of strains resistant to antiviral drugs increases considerably (Englund *et al*, 1990; Christophers *et al*, 1998; Morfin *et al*, 2000; Danve-Szatanek *et al*, 2003; Morfin and Thouvenot, 2003). Resistance to ACV is a major concern for marrow transplantation (Danve-Szatanek *et al*, 2003; Morfin and Thouvenot, 2003). In HIV-infected patients the prevalence of ACV resistance has decreased from 7% to 3.4% during the last 10 years (Englund *et al*, 1990; Christophers *et al*, 1998; Danve-Szatanek *et al*, 2003), probably as a consequence of a reduction in the frequency and severity of opportunistic viral infections since the introduction of highly active antiretroviral therapy (HAART) (Ledergerber *et al*, 2000).

The increasing use of ACV has raised the concern of a growing incidence of ACV-resistant infections. However, literature data do not indicate any increase in the prevalence of resistant HSV in either immunocompromised or immunocompetent population in the past 20 years (Bacon *et al*, 2003). Resistant HSV can develop spontaneously, reflecting the natural variability of the HSV population, as evidenced by the detection of ACV-resistant HSV in patients who had not been treated with this agent (Christophers *et al*, 1998; Sande *et al*, 1998). Properties of the virus, host and these antivirals may explain the apparent rarity of acquired and primary resistance to ACV or penciclovir (Bacon *et al*, 2003). ACV-resistant HSV mutants are generally less virulent than wild-type virus, and less likely to reactivate from latency and replicate at the periphery (Coen, 1994), all of which will reduce the likelihood of transmission. HSV infections, particularly HSV-1 infections, have a relatively long interval between initiation of infection in a person and subsequent transmission to another person; therefore, the dynamics of phenotypic change for HSV within the population are slower than for viruses which are more readily transmissible. The integrity of the host immune response has a critical effect on the severity of infection and the risk of clinical resistance. Because HSV is cleared rapidly by the immune system, there is a limited time when selection of resistant virus can occur in the treated host (Bader *et al*, 1978). The immune system would clear resistant virus just as efficiently as it would clear sensitive virus, ensuring that resistant HSV is typically transient in immunocompetent patients (Ellis *et al*, 1987). Moreover, the majority of mutants resistant to ACV or penciclovir have reduced pathogenicity due to a deficiency of TK. Mutants selected in response to treatment with a compound with a different mode of action could be as pathogenic as wild-type virus (Bacon *et al*, 2003). The selective pressure resulting from treatment with ACV or penciclovir (or their prodrugs) is another important consideration. In the absence of antiviral treatment, selection of the resistant virus does not occur, but when antiviral activity is completely effective, such that there is no viral replication, there can be no selection for antiviral resistance (Richman, 1996). Selection of resistant virus can therefore occur only when there is sufficient viral replication despite the presence of the antiviral. Treatment with ACV or penciclovir reduces, but does not completely prevent, virus shedding in patients with oral HSV infection (Spruance *et al*, 1997), probably because of poor absorption of antiviral, lack of compliance with therapy, or occurrence of suboptimal antiviral concentrations between doses. The selective pressure for resistance arising from the use of these antivirals does not appear to be high as their effects on virus replication *in vivo* are relatively modest (Bacon *et al*, 2003).

It would then be the case that HSV could develop resistance to ACV and related agents, but this is uncommon and perhaps likely to be as great as clinical common will has been expected.

Conclusion

To date, systemic antiviral therapy has been widely accepted as effective for primary herpetic gingivostomatitis. However, only three RCTs suggested that oral ACV may be helpful in reducing the duration of clinical symptoms if started during the first days of onset, but the optimal timing and dose of antiviral therapy differ. The effectiveness of other antiviral drugs has never been

Table 8 Suggested therapy of HSV-1 infection (based upon available data)

Disease	*Type of patient*	*Drug used*	*Dose*	*Route of administration*	*Timing*
PHGS[a]					
	A[b]	Aciclovir suspension – tablets	200 mg	By mouth	5 times daily for 5–7 days
	B[b]	n.u.	n.u.	n.u.	n.u.
RHI[c]					
	A	Aciclovir 5% cream	1 application	Topically	Every 3–4 h for 5 days
		Aciclovir tablets	200 mg	By mouth	5 times daily for 5–7 days
	B	Aciclovir 5% cream (little benefit)	1 application	Topically	Every 3–4 h for 5–7 days
		Aciclovir tablets	400 mg	By mouth	5 times daily for 10 days
	A	Penciclovir 1% cream	1 application	Topically	Every 2 h for 5 days
	B	n.u.	n.u.	n.u.	n.u.
	A	Valaciclovir tablets	2 g	By mouth	2 times daily for 1 day
	B	n.u.	n.u.	n.u.	n.u.
	A	n.u.	n.u.	n.u.	n.u.
	B	Famciclovir tablets	500 mg	By mouth	2 times daily for 7 days
PT[d]					
	A	Aciclovir tablets	400 mg	By mouth	2 times daily for ?? days
		tablets	??	By mouth (preferred)	??
	B	infusion	??	Intravenously	??
	A	n.u.	n.u.	n.u.	n.u.
	B	Famciclovir tablets	500 mg	By mouth	2 times daily for ?? days
	A	tablets	1–2 g	By mouth	??
	B	Valaciclovir tablets	0.5–1 g	By mouth	2–3 times daily for ?? days

?? = according to different situation and to the choice of the doctor; n.u. = not used.
[a]Primary herpetic gingivostomatitis.
[b]A = immunocompetent, B = immunocompromised.
[c]Recurrent herpetic infection.
[d]Prophylactic treatment.

fully established for HSV-1. However, antivirals that increase the bioavailability of ACV, such as valaciclovir and famciclovir, may be of potential benefit as they can be administered less frequently, thereby improving patient compliance. There is a need to undertake RCTs that compare ACV with these agents in the treatment of primary herpetic gingivostomatitis.

Aciclovir (5%) cream seems to be the accepted standard therapy for herpes labialis, being both effective and well tolerated. Recently, penciclovir cream (1%) has also been proposed as effective treatment. Four RCTs have demonstrated the efficacy of ACV cream, and four RCTs have reported that penciclovir cream outperformed the placebo in reducing the signs and painful symptoms of herpes labialis. RCTs that compare ACV (5%) cream with penciclovir cream (1%) are required to establish which of these two agents offers the greatest clinical benefit. Other drugs for the treatment of herpes labialis (e.g. foscarnet, n-docosanl, IDU 15% in DMSO and tromantadine hydrochloride) seem to be less effective than ACV and penciclovir. Systemic ACV may be effective in reducing the duration of painful symptoms and healing time of herpes labialis, but the optimal timing and the dose of the drug are uncertain. Valaciclovir may reduce the duration of herpes labialis, while famciclovir seems to have little clinical benefit. However, studies directly comparing different antivirals are needed.

In immunocompromised groups, oral ACV seems to be the drug of choice for recurrent HSV-1 infection, but recently famciclovir has been found to be of benefit and has the convenience of less frequent dosing than ACV. Topical treatment for these patients is usually of little clinical benefit.

There is some, albeit limited, evidence that prophylactic oral ACV may reduce the frequency and severity of recurrent attacks of herpetic infection in immunocompetent patients, but the optimal timing and duration of treatment are unclear. Prophylactic use of ACV can also be of clinical advantage in immunocompromised patients. Although both oral and intravenous ACV are beneficial, the former should be preferred for less adverse reaction. In addition, the good efficacy and safety of oral valaciclovir has been fully demonstrated. The optimal dose and timing of oral/systemic ACV or oral valaciclovir still remains to be established, but it has been shown to be of clinical efficacy for the prophylactic therapy of HSV-1 infection in immunocompromised groups.

To date, there has been no extensive survey of the rate of emergence of drug-resistant HSV isolates according to the duration of antiviral therapy. Among immunocompetent patients, resistance to ACV is very rare and the increasing use of ACV, especially for prophylactic therapy during bone marrow transplantation, has not resulted in a notable increase in the prevalence of HSV in immunocompromised patients.

The aim of this review was to provide a review of current therapy of HSV-1 infection. Table 8 provides suggested protocols for the common clinical presentations of HSV-infection. However, in view of the availability of newer therapies, there is a need to undertake additional RCTs to establish the most appropriate (and safe) means of treating and preventing

HSV-1 infection in both immunocompetent and immunocompromised persons.

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