Acta Derm Venereol 2010; 90: 122–130

REVIEW ARTICLE

Prevention of Ulcerative Lesions by Episodic Treatment of Recurrent Herpes Labialis: A Literature Review

Johan HARMENBERG[1,2], Bo ÖBERG[1,3] and Spotswood SPRUANCE[4]
[1]Department of Microbiology, Tumor and Cell Biology, Karolinska Institute, Stockholm, [2]Gungner Medical AB, Karolinska Institutet Science Park, Stockholm, [3]Medivir AB, Huddinge, Sweden, and [4]Department of Internal Medicine, University of Utah, Salt Lake City, Utah, USA

There are substantial difficulties involved in carrying out clinical studies of recurrent herpes labialis, since the disease has a rapid onset, short-lasting viral shedding period and is rapidly self-healing. The aim of this paper was to critically assess published reports of episodic treatment of herpes labialis and to review biological and methodological problems involved in such studies. Limited, but statistically significant, results have been shown with topical antivirals, such as acyclovir and penciclovir, improving healing times by approximately 10%. Orally administrated antivirals, such as valaciclovir and famciclovir, have subsequently found clinical use. However, these two oral medications have different profiles in phase 3 studies. Famciclovir showed additional improvement of efficacy in terms of lesion healing time, but no effect on prevention of ulcerative lesions, while valaciclovir appeared to have similar efficacy to that of acyclovir cream on lesion healing, but some additional efficacy with respect to prevention of ulcerative lesions. A formulation of acyclovir/hydrocortisone showed further improvement in prevention of ulcerative lesions, while retaining efficacy with respect to lesion healing. ***Key words: herpes labialis; prevention; herpes simplex virus type 1; treatment.***

(Accepted November 10, 2009.)

Acta Derm Venereol 2010; 90: 122–130.

Johan Harmenberg, Karolinska Institutet, Gungner Medical AB, Karolinska Institutet Science Park, SE-171 77 Stockholm, Sweden. E-mail: johan.harmenberg@gungner.eu

Recurrent herpes labialis is a common infection that affects one-third of the population in the Western world (1). The great majority of cases are caused by herpes simplex virus type 1 (HSV-1). Herpes simplex virus type 2 (HSV-2) has been reported to cause some episodes (2).

Following primary infection in the oral cavity, often occurring at an early age, the virus establishes a chronic, latent and life-long infection in sensory ganglia, predominantly the trigeminal ganglion. At a later date, the virus may be reactivated and travel back to the oral mucosa, perioral skin and/or labial surfaces, where it replicates, producing a clinical episode of recurrent herpes labialis. Primary infection is characterized by a relatively long-lasting viral multiplication and viral shedding period (1, 3, 4). Following termination of the viral replication by the primary immune response, the lesions heal rapidly. The recurrent episode differs from the primary episode in that the virus is typically cleared much more rapidly (within 3 days or less) due to the rapidly deployed acquired immune response, which is already primed after previous episodes (1, 3, 4). However, although in recurrent episodes, the immune response is much quicker and more effective, it is also the cause of most of the clinical symptoms of pain, redness and swelling, through the inflammatory response to the virus.

A recurrent herpes lesion progresses through certain distinct lesion stages (1, 3). These stages occur in sequence: prodrome, redness, papule, vesicle, ulcer, hard crust, dry flaking/residual swelling, and normal skin (healed). Some stages may be short lasting and may go unnoticed. The disease severity is maximal during the "true disease" stages (the vesicle, ulcer and crust stages), which have also been called ulcerative or classical lesions. A lesion may progress through any or all of the stages of prodrome, redness and papule without progressing to vesicles, ulcers or crusts. These are called non-ulcerative lesions or aborted lesions. The disease severity of the non-ulcerative lesions is significantly less than for ulcerative lesions.

Since the viral multiplication is also short-lasting, potent antiviral drugs, such as acyclovir and penciclovir (and their prodrugs valciclovir and famciclovir), show only a limited reduction in the lesions' healing time, of approximately 10%, as the primary benefit. New data have provided the scientific background to a new treatment modality; prevention of herpes labialis outbreaks by episodic treatment. This paper provides a comprehensive review of the recent advances in the pathology and epidemiology of recurrent herpes labialis, the scientific background of the new treatment modality, and a critical review of major trials in the area. Factors important for the assessment and design of randomized clinical trials are discussed.

METHODS

Extensive Medline searches were performed to identify all scientific articles assessing the percentage of a population experiencing

different frequencies of clinical herpes labialis episodes (number of episodes per year). The results are shown in Table I.

The present review includes all major clinical studies in the field of episodic antiviral treatment of recurrent herpes labialis. Only field studies were included (excluding studies of ultraviolet light-induced HSV). These were defined as: (*i*) all phase 3 studies; and (*ii*) other major important studies. There was only one study in this latter category; the large phase 2 studies of iontophoretic administration of acyclovir (5). This study was included since the procedure creates a very large local concentration of acyclovir in the skin. This study population was used for Tables II–IV.

Under the assumption that the probability of an episode of herpes labialis is independent from other episodes, we fitted the data available to the exponential distribution with cumulative distribution function $c_0(1-e^{-\lambda * x})$, where c_0 is the proportion population susceptible to herpes/total population, e is the mathematical constant, $e^{-\lambda}$ is the probability of a herpes outbreak for an individual in the population *that is susceptible* to herpes, and x is the number of outbreaks (6).

HERPES LABIALIS IS COMMON AND MANY SUFFERERS HAVE FREQUENT RECURRENCES

Most patients are infected early in life (3). The incidence of infection increases steadily with age, reaching 80–90% among those 50 years or older. Among the total adult population, 30–45% report a history of symptomatic herpes labialis (Table I). A study in Sweden with 3,597 respondents suggests that the lifetime experience of symptomatic herpes labialis approaches 40% (7).

It has been reported that 1.1% of a population 10 years of age and older will have ongoing herpes labialis at any one time (8). Another study investigating 20,333 individuals showed that 3.1% of the population had ongoing herpes labialis at the time of assessment (9). A more recent study showed that 1.3% of the adult and 1.4% of the elderly population had ongoing herpes labialis at the time of examination (10).

Publically available studies are mostly retrospective surveys. The only exception is the small Australian study (11). None of the studies have attempted to estimate the total disease burden of herpes labialis. The largest study was performed by Axell & Liedholm in Sweden (9) (Table I). Due to the collection procedure in the study, it is likely that less frequent episodes were under-reported. In order to assess the total disease burden in the population, the available data from the Swedish study were fitted to the exponential distribution (i.e. to the cumulative distribution function equation), $c_0(1-e^{-\lambda * x})$, under the assumption that the probability of an episode of herpes labialis is independent of other episodes (courtesy of Karl G. Harmenberg). The model suggested that 3.5% of an adult population experience one episode of herpes labialis per year and 2.7% experience two episodes. The model further suggests that 2.0, 1.6, 1.2, 0.9, 0.7, 0.5, 0.4, 0.3 and 0.2%, experienced 3 through to 11 episodes per year, respectively. The model suggests that approximately 8.6% of the population has 3 or more episodes of herpes labialis every year and 600,000 episodes occur in a population of 1,000,000 (in individuals with one or more episodes per year). Most of the other studies report higher rates than the Swedish study, suggesting that it is a conservative assumption to use data from this study.

Even though there naturally are severe limitations in this type of retrospective study, all data support that there are a very large number of herpes labialis episodes in any given population.

IMPORTANCE OF "FALSE PRODROMES"

Since the time period from first sign or symptom to the tissue damage of the vesicular stage is very short (approximately 24 h or less), the window to initiate therapeutic intervention is narrow and early treatment is key to any therapeutic effect. This was not clearly recognized in the early development of treatment for herpes labialis, thus explaining the variability in efficacy seen in studies from the 1980s and early 1990s. The more recent large trials have all recognized this issue and have all attempted early patient-initiated trial designs. In the first large-scale herpes labialis study, the penciclovir cream study, the patients were instructed to apply cream within one hour of the first sign or symptom of a recurrent herpes labialis regardless of disease stage (Table II) (12). The investigators found

Table I. *Occurrence of recurrent herpes labialis in different groups. Only studies listing the frequency of episodes have been included*

Ref.	Population	*n*	History of recurrent HSV (%)	Episodes per year (% of the total population)								
				< 0.5	0.5	1	2	3	4	5–6	7–11	≥12
(13)	Students (US)	1,788	38.2	10.6		14.0			11.5			2.1
(14)	Students (US)	343	31.5		18.6	10.2			2.7			
(14)	Hospital patients (US)	242	44.6		17.9	18.8			7.9			
(15)	Blood donors (US)	446	32.9			16.0		11.6		5.3		
(9)	General adult population (SWE)[a]	20,333	17.4		2.0		9.8			4.3		1.3
(16)	General adult population (UK)	1,855	42.6	14.2			22.8		4.6		1.0	
(17)	Multinational[b]	10,532	30.1				16.0			6.8		7.3
(11)	Hospital staff (AUS)[c]	347	33.7			27.1	4.3	0.6	0.3	0.3	0.6	

[a]Lifetime experience not assessed resulting in lower frequencies in individuals experiencing < one episode per year. At the time of examination, 3.1% of the population showed ongoing lesions.

[b]Composite from 21 countries. Third world countries tend to show lower rates of herpes labialis. Patients with < one episode per year were not reported.

[c]The only prospective study. 347 persons from the hospital staff were followed during 12 mo. and lesions were assessed and virological samples obtained.

Table II. *The influence of different treatment instructions on the frequency of reported false prodromes*

Ref.	Instruction to patients	False prodromes (%)[a]
(12)	Initiate within 1 hour. All stages allowed.	15.8–16.7
(47)	Initiate within 1 hour but before papule stage	15.8
(5)	Present to clinic with redness or papule	19.9
(18)	At earliest prodrome or redness. Patients with papules or vesicular lesions should not apply.	25.9
(19, 27)	At earliest prodrome. Patients with clinical signs should not apply.	33.9–38.0

[a]Reported false prodromes measured as non-ulcerative lesions/all treated lesions of patients in the placebo groups of large important trials.

that approximately 16% of patients in the placebo group failed to develop ulcerative lesions. These events have been called "false prodromes" and their pathogenesis is unclear. It has been described that recurrences can occur without any clinical signs, only as asymptomatic virus shedding. It is therefore possible that false prodromes may constitute recurrences that normally do not develop into clinical lesions. Since patients are instructed to self-initiate treatment upon prodromes, it is possible, however, that some patients initiate treatment on conditions that do not constitute a clinical herpes recurrence. Support for the latter view is shown in Table II, where the "% false prodromes" is shown for all larger herpes labialis trials. It can be seen that the "% false prodromes" appear to be related to the instructions to patients. Three pivotal trials instructed patients to start treatment on prodromes only; thus not allowing any clinical signs at the time of treatment initiation. These three studies reported an incidence of "false prodromes" ranging from 33.9% to 38.0%. Even though it can be assumed that these episodes should be evenly divided between the study groups, it is noteworthy that perhaps as much as one-third of the patients may not have any documentation of the required condition. It should, however, be noted that regulatory authorities around the world have approved the use of patient-initiated treatment (without prior diagnosis) and thus accepted the "false prodromes". The frequency of "false prodromes" is of less importance when the primary objective is healing time or episode duration, but it becomes important when assessing prevention of episodes developing into ulcerative lesions.

IMPORTANCE OF LESION SIZE

There are three measurable features (apart from clinical symptoms such as pain and tenderness) that categorize the clinical severity of herpes labialis: incidence of ulcerative lesions, lesion duration and lesion size. All large trials have measured incidence and lesion duration, while only one major trial has measured the lesion's size. This could be of importance since any benefit detected with either incidence or lesion duration could theoretically be offset by a worsening of the lesion's size (18). There are presently no reasons to suspect that lesion size may be adversely affected by antiviral treatment, but due to lack of data this cannot be excluded. Again, regulatory authorities around the world have approved a number of treatments for herpes labialis without data about lesion size.

PREVENTION ASSESSED

The prevention of ulcerative lesions with early episodic treatment is naturally of primary importance for herpes labialis sufferers and more important than a small re-

Table III. *Prevention results in large important studies. The acyclovir cream studies did not specify data with respect to prevention and was thus not included in the table. It was however noted that "acyclovir cream did not prevent the development of classical lesions" (26)*

Ref.	Treatment	Initiated treatment (*n*)	Ulcerative lesions (%)	Increased non-ulcerative lesions by treatment (%)	Protected from ulcerative lesions (%)	Hazard ratio	*p*-value
(12)	Penciclovir cream	782	84.8	–3.8	–0.7		NA
	Placebo	791	84.2				
(39)	Penciclovir cream	1516	82.7	3.1	0.6		NA
	Placebo	1541	83.3				
(19), Study 1	Valaciclovir, 1 day	311	55.6	16.7	10.3	1.32	0.096
	Valaciclovir, 2 days	299	53.5	22.3	13.7	1.38	0.061
	Placebo	292	62.0				
(19), Study 2	Valaciclovir, 1 day	298	56.7	22.5	12.3	1.39	0.054
	Valaciclovir, 2 days	339	56.6	22.7	12.4	1.41	0.036
	Placebo	317	64.7				
(27)	Famciclovir 1500 mg single dose	227	67.0	–2.4	–1.2		NA
	Famciclovir 750 mg twice per day	220	71.4	–15.4	–7.9		NA
	Placebo	254	66.1				
(5)	Iontophoresis of 5% acyclovir	99	80.8	27.1	6.0		NA
	Placebo	100	86.0				
(18)	Acyclovir/hydrocortisone	601	57.7	63.3	22.1		<0.0001
	Acyclovir	610	64.6	36.7	12.8		
	Placebo	232	74.1				

NA: not available

Table IV. *Episode duration and lesion healing results in large important trials. Episode duration is measured from initiation of treatment to loss of hard crust in patients with ulcerative lesions and to normal skin in patients with non-ulcerative lesion. Lesions healing is measured from initiation of treatment to loss of hard crust in patients with ulcerative lesions*

Ref.	Treatment	Parameter	Median duration (days)	Median improvement (%)	Hazard ratio	*p*-value
(12)	Penciclovir cream	Lesion healing	4.8	12.7	1.33	< 0.001
	Placebo		5.5			
(39)	Penciclovir cream	Lesion healing	4.6	14.8	1.31	0.0001
	Placebo		5.4			
(26), study 1	Acyclovir cream	Episode duration	4.3 (Mean)	10.4 (Mean)	1.23	0.007
	Placebo		4.8 (Mean)			
(26), study 2	Acyclovir cream	Episode duration	4.6 (Mean)	11.5 (Mean)	1.24	0.006
	Placebo		5.2 (Mean)			
(19), study 1	Valaciclovir, 1 day	Episode duration	4.0	20.0		0.001
	Valaciclovir, 2 days		4.5	10.0		0.009
	Placebo		5.0			
(19), study 2	Valaciclovir, 1 day	Episode duration	5.0	9.1		< 0.001
	Valaciclovir, 2 days		5.0	9.1		< 0.001
	Placebo		5.5			
(27)	Famciclovir 1500 mg single dose	Lesion healing	4.4	29.0	1.64	< 0.001
	Famciclovir 750 mg twice per day		4.0	35.5	2.05	< 0.001
	Placebo		6.2			
(5)	Iontophoresis of 5% acyclovir	Lesion healing	5.8	15.7		0.03
	Placebo		6.9			
(18)	Acyclovir/hydrocortisone	Lesion healing	5.7 (Mean)	12.3		< 0.01
	Acyclovir		5.9 (Mean)	9.2		
	Placebo		6.5 (Mean)			

duction in the duration of episodes. Since prevention cannot be distinguished from "false prodromes" in a clinical setting, it is of importance to use available data with caution and to clarify the necessary assumptions. One way is to compare the fraction of non-ulcerative lesions in the different treatment groups (19). Assessing this fraction in the placebo group naturally gives the frequency of "false prodromes" in a particular study setting. This approach is difficult, since, as has been discussed previously, the frequency of "false prodromes" appears to be dependent on the instructions to the patients, thus making comparison across studies problematic or impossible. For example, if placebo treatment produces 15% aborted lesions (false prodromes) and active treatment shows 30% aborted lesions, the improvement would then be 100%. A better assessment of clinical benefit would be to compare *the fraction of patients who develop ulcerative lesions in spite of treatment with study medication*. Using the same example as stated above, we would then compare 85% of placebo patients with ulcerative lesions with 70% in the group receiving active treatment. The improvement would then be (85–70)/85 = 18%, not 100%. Table III shows critical prevention data from a number of large or important studies.

HIT HARD, HIT EARLY

The results of treating recurrent herpes labialis with antiviral agents during the first decades after the introduction of acyclovir were disappointing, since the benefits were modest and did not match the results obtained in animal models (for reviews see (20–22)). Penetration through the outer layers of the skin (stratum corneum) was identified as a key issue, as well as time of initiation of treatment. Viral multiplication in the skin is maximal during the first 24–48 h of a recurrent episode of herpes labialis (1, 4). Since the initial part of the viral multiplication could be asymptomatic, early initiation of treatment at symptom start is therefore of key importance. Both these issues were addressed in the pivotal valaciclovir studies, which targeted both healing and prevention (19). The valaciclovir studies were the first studies showing signs of efficacy with respect to prevention. Since acyclovir was administrated orally as the prodrug valaciclovir, the skin penetration issue was no longer relevant. Studies in nude mice have shown that oral administration of valaciclovir shows similar target site concentration for 50% inhibition of primary HSV infections (0.25 μg/ml in the basal cell layer of the epidermis) as 5% acyclovir cream (23, 24). After systemic administration of acyclovir, the skin target site drug concentration is expected to be equal to the steady state plasma concentration. Administration of 200 mg of oral acyclovir 5 times daily to humans resulted in mean steady-state concentrations of 0.8 μg/ml (peak) and 0.5 μg/ml (trough); thus roughly similar to the effective levels found in the nude mice (25). Since oral administration of valaciclovir (1 g four times daily) results in approximately six times higher systemic exposure than oral 5 × 200 mg acyclovir (25) it is reasonable to assume that oral administration of valaciclovir would result in higher concentration in the skin target site in comparison with topical 5% acyclovir cream. In addition, acyclovir is believed to reach the

target area in the skin significantly earlier when administered as oral valaciclovir compared with acyclovir cream. The data from the valaciclovir studies showed 10–14% increased protection of ulcerative lesions by valaciclovir (*p*-values ranging from 0.036 to 0.096), which appeared better than the acyclovir cream data (19). Published results with acyclovir cream on this point stated that "Acyclovir cream did not prevent the development of classical lesions" (26). While we were not given the raw data, if is fair to assume from this statement that neither statistically significant differences nor any trend toward treatment group differences were identified. Even though the valaciclovir prevention data were borderline significant, the US Food and Drug Administration (FDA) and other regulatory authorities did not approve the prevention indication. Even though oral valaciclovir appeared to be more efficient than acyclovir cream in terms of prevention, the two medications appeared to have similar efficacy in terms of episode duration, both with a reduction of approximately 10%. It should be noted that episode duration is the time from treatment initiation to loss of hard crust for ulcerative lesions and from time of treatment initiation to normal skin for non-ulcerative lesions. All patients and all lesions can therefore be accounted for with this parameter.

Oral famciclovir (prodrug of penciclovir) is generally believed to have potency similar to that of valaciclovir in the treatment of recurrent herpes labialis. The results from the pivotal trials were therefore surprising (27). The primary end-point for these studies was lesion healing, defined as the time from the start of treatment to loss of hard crust for ulcerative lesions. Patients with non-ulcerative lesions were therefore not included and the primary assessment was therefore by definition a subgroup analysis. Nevertheless, the subgroup of patients with ulcerative lesions treated with famciclovir reported a 29–36% reduction in lesion healing time. This favorable effect did not, however, translate into any reported effect on prevention, and the fraction of patients protected from ulcerative lesions was not increased and, if anything, decreased by treatment with famciclovir (Table III). Again, the results point towards the importance of assessing all clinically important parameters side by side.

IMPORTANCE OF DRUG CONCENTRATION AT THE SITE OF VIRAL MULTIPLICATION

HSV grows in the lower layers of epidermis in the vicinity of the basal membrane. As discussed earlier, viral multiplication is a very early event in a herpes labialis episode and distributing antiviral agents to the site of viral replication as early as possible is therefore important. The concentration-time curve at the site of activity following topical application is primarily limited by the outer layer of the epidermis, the stratum corneum. Similarly, the concentration-time curves following oral application are limited by the rate and speed of absorption from the gastrointestinal system. It is, however, not possible directly to study the concentration of antiviral agent in the lower layers of epidermis, since the capillaries end in dermis, but the concentration at steady state can be assessed using indirect means, as discussed in the previous section.

Studies using primary HSV infection in guinea pigs have clearly shown that antiviral efficacy of topical antiviral treatment is closely related to skin penetration (28–30). The skin penetration, and thus also the target site concentration, have been shown to vary according to the vehicle of the topical preparations (28–30). It is therefore reasonable to assume that the target site concentration is critical for antiviral efficacy, at least when discussing primary infection with comparatively long viral replication period. Recurrent infections with much shorter viral replication period combined with a more vigorous immune reaction are a more complex situation.

From the discussion above, it is reasonable to suggest that oral valaciclovir delivers approximately six times more acyclovir to the site of activity than acyclovir cream. It was therefore expected that this would result in clearly improved efficacy in recurrent herpes labialis, especially since the valaciclovir studies focused to greater extent than the acyclovir cream studies on early aggressive treatment, as discussed previously. The results indicated that the two treatments had similar efficacy with respect to episode duration, while the valaciclovir study reported a trend of prevention (19, 26). There has been no comparative trial of valaciclovir vs. acyclovir cream, and it is unlikely that it will ever be done. Even if, as has been suggested, the valaciclovir results are superior to those of acyclovir cream, it is unclear whether this hypothetical difference depended on higher concentration at the site of activity or trial design (the earlier treatment initiation in the valaciclovir trials).

Penetration of topically applied acyclovir can be further improved by the application of iontophoresis (23, 31, 32). Preclinical studies have shown that the flux of acyclovir through skin can increase dramatically while the accumulation in the skin only is more modest (31). A useful device for the iontophoretic delivery of acyclovir cream has been studied clinically in the treatment of herpes labialis (Table III and IV) (5). The study design was challenging for the investigators, since all recruited patients had to have clear signs of a herpes labialis recurrence. In total, 199 patients were included, with 72% in the papule stage and the rest in the erythema stage and the patients were randomized to acyclovir or placebo. The results showed a 16% reduction in lesion healing time in the total population, that appears to be similar or better than acyclovir cream trial

results, and a weak trend with respect to the prevention end-point. It should again be noted that most patients in the iontophoresis trials were in the papule stage, thus these results are more impressive. The study generated some interesting subgroup assessments. Fourteen of the 26 patients recruited in the erythema stage developed ulcerative lesions, compared with only 7 of 29 in the placebo group. Results from small subgroups should, as always, be interpreted with caution, and results from larger studies are eagerly awaited.

IMPORTANCE OF THE IMMUNE SYSTEM

The fundamental difference between primary and recurrent HSV infection was not initially fully appreciated during the early development of antiviral drugs such as acyclovir. Primary infections are, as mentioned previously, characterized by duration of viral multiplication in the skin of approximately 2 weeks (1, 4, 33). After the virus is cleared by the immune system, the lesions heal rapidly (1, 4, 33). Given this long duration of viral multiplication, it is not surprising that treatment with antiviral drugs, such as acyclovir, could give clinical benefits approaching 50% in terms of lesion healing time and viral shedding duration as shown for primary genital herpes infections (34). These results were expected, since animal models mimicking primary herpes simplex infections also showed results in a similar range (33, 35, 36).

Recurrent HSV infection occurs in the presence of an immune system capable of delivering an immediate and vigorous response to the virus. The virus is therefore cleared much more rapidly in recurrent HSV infections (often less than 48–72 h) compared with the primary infection (1, 4). Even though the virus is cleared rapidly due to the vigorous response from the immune system, symptoms remain for approximately one week after the time when virus no longer can be detected. Recurrent ulcerative HSV lesions typically take 7–10 days to heal (1, 3, 4), while the healing time of all episodes (a mix of ulcerative and non-ulcerative lesions) is 5–6 days.

Since antiviral drugs such as acyclovir were successful in providing clinically benefit in terms of healing time and viral multiplication duration in primary herpes simplex infections both in humans and animal models, it was expected that a similar benefit should be detected also in clinical studies of recurrent HSV infections. The early clinical trials indicated, however, a maximally possible healing time reduction of only approximately 10–15% (12, 26, 37–41).

COMBINATION TREATMENT

It is now well established that patients with recurrent herpes simplex infections have two medical problems: the virus multiplication and the overreacting immune system. However, any hypothesis that simultaneous treatment of the respective conditions would improve clinical outcomes was previously impossible to test as there were no animal models mimicking the recurrent herpes simplex infection. The breakthrough came with a refinement of an existing zosteriform animal model in mice in which the virus is inoculated in the skin of the neck of animals (42).

Animal model: Following infection, the virus is transported through the nerves to the corresponding ear of the animals. Replicating virus could be shown in the ear tissue starting exactly 4 days after the original infection in a reproducible manner. The advantage of this model is that, during the time when the virus is transported through the nerves, it is also protected from the immune system. It was therefore possible to give the mice a full and HSV-specific immune response on day 2 after infection using an adoptive transfer of immunity from other mice. The cervical lymph nodes were removed from the donor mice 7 days after inoculation of HSV-1 in the ears of the mice. Recipient mice were given 3.6×10^6 live lymph node cells via the coccygeal vein. This model thus has the hallmarks of a recurrent infection, the virus is transported through the nerves and at the time of initiation of virus multiplication in the ears, the mice have a full HSV-specific immune system. A further relief was that traditional antiviral treatments, such as acyclovir, penciclovir and foscarnet, showed only 10–15% benefit on measurable parameters (similar to the benefit found in clinical trials in patients with recurrent HSV infections) (43, 44). Since the thin mice ears swell due to inflammation, measuring the thickness of the ears could be used as a convenient and sensitive parameter of inflammation.

Using the mouse-ear model of recurrent HSV, it was shown that combinations of acyclovir and steroids could provide benefit that was superior to that of combinations of acyclovir and other tested immune modulators (43, 44). The results also suggested that combinations of acyclovir and hydrocortisone appeared to be somewhat superior to that of acyclovir in combination with more potent steroids. It should, however, be noted that mice are generally thought to be more sensitive to the action of steroids than humans. In the mouse-ear model, potent steroids could stimulate virus multiplication to such an extent that the effect of acyclovir treatment was diminished. The combined experience with the mouse-ear model indicated that the expected clinical benefit would approach 50%. As discussed previously, benefit could be assessed clinically with three parameters; incidence of ulcers, healing time and lesion size. Due to the design of the mouse-ear model it was, however, not possible to predict which parameter(s) would be influenced most by a combination treatment.

Human trials: The results of the mouse-ear model immediately stimulated clinical research to test the two-problem hypothesis. Spruance & McKeough (45) exposed 49 patient to experimental UV radiation, of which 29 patients developed recurrent herpes labialis. Patients were instructed to start treatment with either famciclovir (Famvir 500 mg, three times per day orally) and fluocinonide (0.05% Lidex Gel, three times per day topically) or famciclovir in combination with a topical vehicle control within one hour of first signs or symptoms of a herpes labialis episode. The most impressive result of this double-blind randomized pilot study was that episodes treated with the combination of high-dose antiviral drug and potent steroid resulted in non-ulcerative lesions in 41% of patients, compared with 8% of patients treated with antiviral drug only. Further benefits included a reduction in HSV lesion size.

Evans and co-workers (46) exposed 380 patients to experimental UV radiation to induce herpes labialis. Patients were treated with a topical combination of acyclovir and hydrocortisone (ME-609) in comparison with topical placebo. The main result of this double-blind randomized study was that 29% less patients in the combination treatment group developed ulcerative lesions compared with placebo patients. The results from this study together with the previously mentioned study of Spruance & McKeough (45) suggested that the main benefit of early episodic treatment of a combination of an antiviral and a steroid was a reduction in the incidence of herpes labialis.

This conclusion has recently been supported by Hull and co-workers (47) in a double-blind placebo-controlled study of patients with recurrent herpes labialis. A total of 81 patients were randomized, out of whom 42 patients developed signs or symptoms of a recurrence and self-initiated early treatment. Patients were treated with a combination of high-dose oral valaciclovir (Valtrex 2000 mg twice per day, for one day) and potent topical steroid (clobetasol gel 0.05% twice per day, for 3 days) or matching placebo. The results showed that 50% of the patients treated with combination treatment developed non-ulcerative lesions compared with 16% in the control group. In addition, there was a major reduction in lesion size in the combination treated group.

The antiviral-steroid combination hypothesis was tested in a large phase 3 study in which 2,437 adult patients were randomized into the study (Tables III and IV) (18). A total of 1443 patients experienced an episode and initiated topical treatment with either acyclovir cream ($n=610$), placebo ($n=232$) or acyclovir/hydrocortisone combination (ME-609, $n=601$). All preparations contained the same vehicle, which was not identical to the vehicle of acyclovir (Zovirax) cream. The results showed that 42.3% of the acyclovir/hydrocortisone cream (ME-609)-treated patients did not develop an ulcerative lesion, compared with 35.4% of the acyclovir cream-treated patients and 25.9% of the placebo-treated patients. This means that 22.1% of the patients in the acyclovir/hydrocortisone-treated group were protected from developing non-ulcerative lesions compared with the placebo group, and that 12.8% of the acyclovir-treated patients were similarly protected (Table III). The results for the acyclovir/hydrocortisone-treated group (ME-609) was not largely different from the data found in the preceding phase 2 study where 29% of the patients were protected from developing ulcerative lesions (46). It was, however, a surprise that 12.8% of the acyclovir cream-treated patients were protected from ulcerative lesions, since the phase 3 studies of acyclovir cream (Zovirax) failed to show any effect on prevention. The 12.8% protection from ulcerative lesions was in the same order of magnitude as the valaciclovir studies (Table III). A possible explanation could be that the cream vehicle of the ME-609 formulation has shown significantly improved properties in terms of acyclovir penetration compared with the Zovirax vehicle (44). As seen in Table IV, the improved penetration property did not translate into improved lesion healing time. The FDA recently approved the ME-609 formulation of acyclovir/hydrocortisone for "early treatment of recurrent cold sores to decrease the risk of cold sores, and to shorten the healing time for those cold sores which are not prevented". European Authorities have approved this combination with a similar labeling.

FUTURE DIRECTIONS

The principle of using a combination treatment against recurrent labial herpes could also be explored as a treatment of recurrent genital herpes. In view of the similarity between these diseases it seems likely that an early treatment initiation could reduce the incidence of ulcerative lesions in genital herpes. It should, however, be noted that topical treatment only treats the area of application, while oral treatment treats the whole patient. The occurrence of lesions appearing outside of the topically treated area has been estimated to occur in approximately 5% of the patients, which suggest that this problem is of limited magnitude (J. Harmenberg, personal communication).

The use of a mild corticosteroid, such as hydrocortisone, in combination with acyclovir appears to alter the clinical course of herpes labialis for a sizeable proportion of the patients. This naturally opens the way for further improvements in the future, when more potent corticosteroids, as well as corticosteroids with different properties could be tested. An interesting property of corticosteroids is their ability to form skin reservoirs (mainly in stratum corneum) (48–51). Due to the stratum corneum reservoirs, topically applied corticosteroids may exert their effect many hours or days after all of the steroid has been removed from the skin surface.

The presence of reservoir effects may allow for less frequent application of the medication. Potentially only a single application may be sufficient. Preliminary data suggest that the reservoir effect is not so extensive for acyclovir (personal communication J. Harmenberg). If improvements in antiviral/steroid combinations are explored though utilizing the reservoir effect, the acyclovir component may have to be replaced with an antiviral with more extensive reservoir effect.

The state-of-the-art end-point of herpes labialis has, over the last decade, been episode duration. Episode duration is measured from the time of the patient-initiated start of treatment of an episode until the time of loss of hard-crust for ulcerative lesions and to normal skin for non-ulcerative lesions. Importantly, the time when skin is "normal" cannot be measured with any precision and is thus subjective and highly variable. A more important problem is that "episode duration" puts equal weight on an ulcerative lesion that is a morbid condition, as a non-ulcerative lesion may be pain-free and hardly noticeable. In addition, since ulcerative lesions are measured only to loss of hard crust stage, which is earlier than to normal skin stage, it is possible to argue that non-ulcerative lesions measured to normal skin stage may have an inappropriately exaggerated weight in the computation of the episode duration statistics. It is clear that the clinical benefit of an agent that shifts ulcerative lesions to non-ulcerative lesions will be under-estimated when episode duration is used as the end-point.

Most of the phase 3 studies have not measured the size of the lesions. Patients would certainly prefer a small lesion to a large one, and this is an important parameter to study, together with prevention and healing time. It is also an important safety measure, since it is, at least theoretically, possible that a medication that increases prevention and/or decreases healing time may increase lesion size in those lesions that develop in spite of treatment. A parameter that deserves to be tested clinically is to measure the size of ulcerative lesions daily (until loss of hard crust) and to add all of these areas together. Patients starting treatment and not developing ulcerative lesions would be given the value zero. Such a parameter would include all of the clinically important features; size, time to healing and prevention of ulcerative lesions and would be a measure of total disease burden. As a further benefit, clinicians would not have to determine a specific time for the gradual process of non-ulcerative lesions healing to normal skin (4, 47, 52).

ACKNOWLEDGEMENTS

We are indebted to Karl G. Harmenberg, Harvard College, Harvard University, Cambridge, Massachusetts, USA for the mathematical modeling cited in the text.

Conflicts of interest: Dr Spruance and Dr Harmenberg serve as consultants to Medivir AB. Dr Öberg is employed by Medivir AB, Sweden. Drs Öberg and Harmenberg own stocks in Medivir AB.

REFERENCES

1. Spruance SL. The natural history of recurrent oral-facial herpes simplex virus infection. Semin Dermatol 1992; 11: 200–206.
2. Wald A, Ericsson M, Krantz E, Selke S, Corey L. Oral shedding of herpes simplex virus type 2. Sex Transm Infect 2004; 80: 272–276.
3. Spruance SL. Herpes simplex labialis. In: Sacks SL, Straus SE, Whitley RJ, editors. Clinical management of herpes viruses. Amsterdam, Washington DC: IOS Press; 1995, p. 3–42.
4. Spruance SL, Overall JC, Jr, Kern ER, Krueger GG, Pliam V, Miller W. The natural history of recurrent herpes simplex labialis: implications for antiviral therapy. N Engl J Med 1977; 297: 69–75.
5. Morrel EM, Spruance SL, Goldberg DI, Iontophoretic Acyclovir Cold Sore Study G. Topical iontophoretic administration of acyclovir for the episodic treatment of herpes labialis: a randomized, double-blind, placebo-controlled, clinic-initiated trial. Clin Infect Dis 2006; 43: 460–467.
6. Ross S. A first course in probability. Upper Saddle River, New Jersey, USA: Pearson Education, Inc., 2006.
7. Löwhagen GB, Bonde E, Eriksson B, Nordin P, Tunbäck P, Krantz I. Self-reported herpes labialis in a Swedish population. Scand J Infect Dis 2002; 34: 664–667.
8. Hellgren L. The prevalence of some skin disease and joint disease in total populations in different areas of Sweden. Proc Northern Dermatol Soc 1962: 155–162.
9. Axell T, Liedholm R. Occurrence of recurrent herpes labialis in an adult Swedish population. Acta Odontol Scand 1990; 48: 119–123.
10. Reichart PA. Oral mucosal lesions in a representative cross-sectional study of aging Germans. Community Dent Oral Epidemiol 2000; 28: 390–398.
11. Hatherley LI, Hayes K, Hennessy EM, Jack I. Herpes virus in an obstetric hospital: I: Herpetic eruptions. Med J Aust 1980; 2: 205–208.
12. Spruance SL, Rea TL, Thoming C, Tucker R, Saltzman R, Boon R. Penciclovir cream for the treatment of herpes simplex labialis. A randomized, multicenter, double-blind, placebo-controlled trial. Topical Penciclovir Collaborative Study Group. JAMA 1997; 277: 1374–1379.
13. Ship II, Morris AL, Durocher RT, L.W. B. Recurrent aphthous uncelations and recurrent herpes labialis in a professional school student population. I. Experience. Oral Surg Oral Med Oral Pathol 1960; 13: 1191–1202.
14. Ship II, Brightman VJ, Laster LL. The patient with recurrent aphthous ulcers and the patient with recurrent herpes labialis: a study of two population samples. J Am Dent Assoc 1967; 75: 645–654.
15. Young TB, Rimm EB, D'Alessio DJ. Cross-sectional study of recurrent herpes labialis. Prevalence and risk factors. Am J Epidemiol 1988; 127: 612–625.
16. Grout P, Barber VE. Cold sores-an epidemiological survey. J R Coll Gen Pract 1976; 26: 428–434.
17. Embil JA, Stephens RG, Manuel FR. Prevalence of recurrent herpes labialis and aphthous ulcers among young adults on six continents. Can Med Assoc J 1975; 113: 627–630.
18. Hull C, Harmenberg J, Arlander E, Aoki F, Darpo B, Levin M, et al. Episodic treatment with topical ACV/hydrocortisone (Lipsovir®) prevents cold sores: a randomized, double-blind, patient-initiated clinical trial. Abstract, 49th Interscience Conference on Antimicrobial Agents and Chemotherapy, September 12–15, San Fransisco, California, USA, 2009.
19. Spruance SL, Jones TM, Blatter MM, Vargas-Cortes M, Barber J, Hill J, et al. High-dose, short-duration, early valacyclovir therapy for episodic treatment of cold sores: results

of two randomized, placebo-controlled, multicenter studies. Antimicrob Agents Chemother 2003; 47: 1072–1080.
20. Elish D, Singh F, Weinberg JM. Therapeutic options for herpes labialis, II: Topical agents. Cutis 2004; 74: 35–40.
21. Elish D, Singh F, Weinberg JM. Therapeutic options for herpes labialis, I: Oral agents. Cutis 2004; 74: 31–34.
22. Moomaw MD, Cornea P, Rathbun RC, Wendel KA. Review of antiviral therapy for herpes labialis, genital herpes and herpes zoster. Expert Rev Anti Infect Ther 2003; 1: 283–295.
23. Imanidis G, Song WQ, Lee PH, Su MH, Kern ER, Higuchi WI. Estimation of skin target site acyclovir concentrations following controlled (trans)dermal drug delivery in topical and systemic treatment of cutaneous HSV-1 infections in hairless mice. Pharm Res 1994; 11: 1035–1041.
24. Mehta SC, Afouna MI, Ghanem AH, Higuchi WI, Kern ER. Relationship of skin target site free drug concentration (C*) to the in vivo efficacy: an extensive evaluation of the predictive value of the C* concept using acyclovir as a model drug. J Pharm Sci 1997; 86: 797–801.
25. Physicians' Desk Reference. Thomson PDR Electronic Library, version 7.0.308a, Thomson Reuters, Montvale, New Jersey, USA, 2009.
26. Spruance SL, Nett R, Marbury T, Wolff R, Johnson J, Spaulding T. Acyclovir cream for treatment of herpes simplex labialis: results of two randomized, double-blind, vehicle-controlled, multicenter clinical trials. Antimicrob Agents Chemother 2002; 46: 2238–2243.
27. Spruance SL, Bodsworth N, Resnick H, Conant M, Oeuvray C, Gao J, et al. Single-dose, patient-initiated famciclovir: a randomized, double-blind, placebo-controlled trial for episodic treatment of herpes labialis. J Am Acad Dermatol 2006; 55: 47–53.
28. Freeman DJ, Sheth NV, Spruance SL. Failure of topical acyclovir in ointment to penetrate human skin. Antimicrob Agents Chemother 1986; 29: 730–732.
29. Freeman DJ, Spruance SL. Efficacy of topical treatment for herpes simplex virus infections: predictions from an index of drug characteristics in vitro. J Infect Dis 1986; 153: 64–70.
30. Spruance SL, Freeman DJ, Sheth NV. Comparison of foscarnet cream, acyclovir cream, and acyclovir ointment in the topical treatment of experimental cutaneous herpes simplex virus type 1 infection. Antimicrob Agents Chemother 1986; 30: 196–198.
31. Padula C, Sartori F, Marra F, Santi P. The influence of iontophoresis on acyclovir transport and accumulation in rabbit ear skin. Pharm Res 2005; 22: 1519–1524.
32. Volpato NM, Nicoli S, Laureri C, Colombo P, Santi P. In vitro acyclovir distribution in human skin layers after transdermal iontophoresis. J Control Release 1998; 50: 291–296.
33. Alenius S, Berg M, Broberg F, Eklind K, Lindborg B, Öberg B. Therapeutic effects of foscarnet sodium and acyclovir on cutaneous infections due to herpes simplex virus type 1 in guinea pigs. J Infect Dis 1982; 145: 569–573.
34. Richards DM, Carmine AA, Brogden RN, Heel RC, Speight TM, Avery GS. Acyclovir. A review of its pharmacodynamic properties and therapeutic efficacy. Drugs 1983; 26: 378–438.
35. McKeough MB, Spruance SL. Comparison of new topical treatments for herpes labialis: efficacy of penciclovir cream, acyclovir cream, and n-docosanol cream against experimental cutaneous herpes simplex virus type 1 infection. Arch Dermatol 2001; 137: 1153–1158.
36. Poli G, Dall'Ara P, Binda S, Santus G, Poli A, Cocilovo A, et al. Value of the dorsal cutaneous guinea pig model in selecting topical antiviral formulations for the treatment of recurrent herpes simplex type 1 disease. Arzneimittelforschung 2001; 51: 433–438.
37. Corey L, Benedetti JK, Critchlow CW, Remington MR, Winter CA, Fahnlander AL, et al. Double-blind controlled trial of topical acyclovir in genital herpes simplex virus infections. Am J Med 1982; 73: 326–334.
38. Corey L, Nahmias AJ, Guinan ME, Benedetti JK, Critchlow CW, Holmes KK. A trial of topical acyclovir in genital herpes simplex virus infections. N Engl J Med 1982; 306: 1313–1319.
39. Raborn GW, Martel AY, Lassonde M, Lewis MA, Boon R, Spruance SL, et al. Effective treatment of herpes simplex labialis with penciclovir cream: combined results of two trials. J Am Dent Assoc 2002; 133: 303–309.
40. Reichman RC, Badger GJ, Guinan ME, Nahmias AJ, Keeney RE, Davis LG, et al. Topically administered acyclovir in the treatment of recurrent herpes simplex genitalis: a controlled trial. J Infect Dis 1983; 147: 336–340.
41. Spruance SL, Crumpacker CS. Topical 5 percent acyclovir in polyethylene glycol for herpes simplex labialis. Antiviral effect without clinical benefit. Am J Med 1982; 73: 315–319.
42. Awan AR, Harmenberg J, Kristofferson A, Field HJ. Herpes simplex virus zosteriform lesions with adoptive transfer of immune cells: a murine model which mimics human recurrent disease. Antiviral Res 1998; 38: 43–53.
43. Awan AR, Harmenberg J, Flink O, Field HJ. Combinations of antiviral and anti-inflammatory preparations for the topical treatment of herpes simplex virus assessed using a murine zosteriform infection model. Antivir Chem Chemother 1998; 9: 19–24.
44. Harmenberg JG, Awan AR, Alenius S, Ståhle L, Erlandsson AC, Lekare G, et al. ME-609: a treatment for recurrent herpes simplex virus infections. Antivir Chem Chemother 2003; 14: 205–215.
45. Spruance SL, McKeough MB. Combination treatment with famciclovir and a topical corticosteroid gel versus famciclovir alone for experimental ultraviolet radiation-induced herpes simplex labialis: a pilot study. J Infect Dis 2000; 181: 1906–1910.
46. Evans TG, Bernstein DI, Raborn GW, Harmenberg J, Kowalski J, Spruance SL. Double-blind, randomized, placebo-controlled study of topical 5% acyclovir-1% hydrocortisone cream (ME-609) for treatment of UV radiation-induced herpes labialis. Antimicrob Agents Chemother 2002; 46: 1870–1874.
47. Hull C, McKeough M, Sebastian K, Kriesel J, Spruance S. Valacyclovir and topical clobetasol gel for the episodic treatment of herpes labialis: a patient-initiated, double-blind, placebo-controlled pilot trial. J Eur Acad Dermatol Venereol 2009; 23: 263–267.
48. Magnusson BM, Cross SE, Winckle G, Roberts MS. Percutaneous absorption of steroids: determination of in vitro permeability and tissue reservoir characteristics in human skin layers. Skin Pharmacol Physiol 2006; 19: 336–342.
49. Pelchrzim R, Weigmann HJ, Schaefer H, Hagemeister T, Linscheid M, Shah VP, et al. Determination of the formation of the stratum corneum reservoir for two different corticosteroid formulations using tape stripping combined with UV/VIS spectroscopy. J Dtsch Dermatol Ges 2004; 2: 914–919.
50. Turpeinen M. Absorption of hydrocortisone from the skin reservoir in atopic dermatitis. Br J Dermatol 1991; 124: 358–360.
51. Vickers CF. Stratum corneum reservoir for drugs. Adv Biol Skin 1972; 12: 177–189.
52. Spruance SL, Hill J. Clinical significance of antiviral therapy for episodic treatment of herpes labialis: exploratory analyses of the combined data from two valaciclovir trials. J Antimicrob Chemother 2004; 53: 703–707.