Advances in Short-Term Therapy for Herpes Labialis

With growth in treatment offerings, clinicians and patients have more options to treat this chronic viral infection.

BY TODD E. SCHLESINGER, MD, FAAD

Herpes simplex virus (HSV) is the most broadly spread virus in the herpes virus family. Ubiquitous and contagious, HSV exists as two types: 1 and 2 (HSV-1 and HSV-2). Usually, HSV-1 is associated with oral and labial disease, while HSV-2 is linked to genital manifestations.[1] About one billion people worldwide have been infected with the herpes viruses. In the United States, approximately 51 percent of persons over 12 years of age are seropositive for HSV-1 alone, 5.3 percent are seropositive for HSV-2 alone, and approximately 17 percent are coinfected with HSV-1 and HSV-2.[2] Recent advances in therapy have shortened the treatment duration needed to control episodic herpes labialis, making therapy more practical. For the purposes of this brief update, I will focus on HSV-1, the more prevalent condition in the United States.

Recurrent HSV infection occurs in the presence of an immune system capable of delivering an immediate and vigorous response to the virus. More rapid clearance (48-72 hours) of the virus occurs in recurrent infections compared to primary infections. However, symptoms remain for approximately one week after the point at which the virus is no longer detectable. Ulcerative lesions often take seven to 10 days to heal, while the healing time of all lesions (ulcerative and non-ulcerative) is five to six days.[2] HSV-1 is a mucocutaneous virus that remains latent in the treminal ganglion and oral mucosa. Reactivation is frequent, but often asymptomatic.[3] Transmission of HSV-1 occurs in the presence of herpes lesions and also during oral shedding, even in the absence of visible oral lesions.

THERAPEUTIC UPDATE

The mainstays of first-line HSV-1 treatment belong to the antiviral class of drugs known as viral nucleoside analogs. Acyclovir and its prodrug valacyclovir remain the most common treatment for recurrent HSV infections in their various forms. Their mechanism of action is the competitive inhibition of viral DNA polymerase, incorporation into the expanding viral DNA chain, and inactivation of viral DNA polymerase. The affinity for virally-encoded thymidine kinase is highly specific, resulting in a low incidence of adverse effects.

PRACTICAL POINTER

Treatment duration for HSV-1 infections has shortened as we have learned more about the disease pattern, site of replication, and time to maximal viral replication with respect to the prodromal symptoms that almost always accompany the onset of an episode. Many good options exist for treating HSV. Putting the decision of when to treat in the hands of the patient could potentially produce better outcomes.

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Originally, treatment with these drugs was given for approximately one week per episode. Acyclovir was initially dosed five times daily, due to low oral bioavailability (10-20 percent) and short plasma elimination half-life. Valacyclovir achieved a 54 percent absolute bioavailability of acyclovir after oral administration, allowing less frequent dosing.[4] However, recognizing that HSV-1 replicates in the basal layer of the mucosa before the onset of signs and symptoms of disease and with maximum replication within the first eight hours after the onset of prodromal symptoms led to the theory that a high and early dose of drug was needed.[5] Studies carried out with valacyclovir established that single-day, high-dose (4g per day) treatment was safe and effective when given at the first sign of an outbreak and shortened the clinical course of the disease.[6] Similar studies were carried out with famciclovir, the oral prodrug of penciclovir, showing that single-day high-dose famciclovir also reduced time to healing of primary vesicular herpes labialis lesions by approximately two days when compared to placebo.[7]

Turning to the site of replication, HSV-1 replicates in the basal layer of mucosa beginning before the first signs of outbreak, or in the prodromal period. Maximum replication occurs within the first eight hours after the onset of prodromal symptoms and is detected in oral mucosa, saliva, and in herpes lesions.[8,9] Recognition of the site of replication led to studies looking at the skin penetration of nucleoside analogs such as acyclovir and penciclovir using a tape stripping method. In a study carried out *in vitro* using harvested skin, penciclovir was found to penetrate more deeply into the dermis than acyclovir, whereas acyclovir remained on the surface. However, the different intracellular half-lives of acyclovir (0.7-1h) and penciclovir (10-20h) may also play a role in the observed concentration differences.[10] Studies have demonstrated that it

is possible to reduce viral replication and hasten lesion resolution with 1% penciclovir treatment beyond the prodromal phase of HSV infection. Superiority over topical acyclovir in terms of a significant decrease in time to lesion healing, lesion area, and pain has been demonstrated.[11]

The need for a more effective topical agent that is as effective as systemic agents, well tolerated, administered at the first sign of prodromal symptoms and that could sustain early and high salivary and mucosal drug levels led to the development of the mucoadhesive buccal tablet (MBT). This unique delivery system allows for the rapid and prolonged release of the active substance in the oral cavity. The efficacy of the delivery system was demonstrated in a study comparing an MBT containing miconazole and miconazole oral gel (MOG) for the treatment of oropharyngeal candidiasis in cancer patients. The authors were able to demonstrate non-inferiority in terms of success rate with a 10-fold lower dose of miconazole (50mg versus 500mg) and once daily administration compared to a four-times-daily schedule with MOG.[12]

Turning to acyclovir, a pharmacokinetic evaluation was conducted comparing acyclovir 50mg and 100mg MBT with acyclovir 200mg oral tablet. Labial mucosa acyclovir concentrations measured using tape-stripping of dry mucosal lip skin and revealed a geometric mean concentration of $361ng/cm^2$ three hours after application of the 50mg MBT and remaining stable up to 18 hours post-dosing. Acyclovir was not detected in any labial samples after oral administration of acyclovir 200mg tablet. Similar results were seen in the evaluation of salivary concentrations, with rapid, high and sustained concentrations of acyclovir detected in saliva that remained above the IC_{50} for HSV for up to 32 hours after application of the 50mg acyclovir MBT. No drug was detected in saliva 10 hours after administration of 200mg acyclovir oral tablet, and saliva concentrations were many times lower. In fact, salivary concentrations of acyclovir fell below the Inhibitory Concentration 50 (IC_{50}) less than four hours after administration.

With respect to plasma concentrations, the concentration profile for MBT demonstrated a sustained release pattern with a delayed onset of detection followed by a low and steady rise before tapering off approximately 35 hours after administration. This is in sharp contrast to the profile seen with acyclovir 200mg oral tablet, which revealed an early rise followed by a rapid decline in plasma concentration then a steady taper over 45 or more hours. An argument can be made that the rapid exposure to high acyclovir concentrations in the saliva and labial mucosa in

the early prodromal stages of an HSV eruption may lead to an increase in abortive lesions and decreased shedding via a reduced viral reservoir in the oral mucosa.[13]

Additionally, trials conducted many years ago evaluated the possibility of retrograde axonal transport of compounds from peripheral nerve endings to the trigeminal ganglia. Using Adriamycin injected into the tongues of mice, it was determined that cytotoxicity occurred in the hypoglossal nerve ganglia, supporting the notion of retrograde axonal transport.[14] These findings suggest that the efficacy of compounds delivered to the oral mucosa via an MBT may extend beyond the nerve endings directly associated with the oral cavity and thus may have implications for using acyclovir 50mg MBT as pre procedural HSV prophylaxis.

Efficacy and safety of acyclovir MBT were evaluated in a large, Phase III trial comparing acyclovir 50mg MBT to placebo in immunocompetent patients with labial herpes with at least four recurrent episodes in the 12 months preceding the study. The primary endpoint of time to healing (TTH) of the primary vesicular lesion at the vermillion border defined as time of treatment initiation to complete loss of crust, was significantly shorter (seven days) in the MBT group than in the placebo group (7.3 days, log rank test P=.015). The proportion of patients with blocked episodes was 24.2 percent higher (P=.042) in the treatment group compared to the placebo group while the median time to recurrence was increased significantly by 40 days (P=.041) in the treatment group compared to the placebo group.

In the subset of patients who self-administered the treatment medication within one hour after prodromal symptoms, the median time to recurrence increased by 54 days (P=.049) compared to the placebo group. The authors speculated that the rapid and high, sustained concentrations of acyclovir in saliva and labial mucosa may decrease the viral reservoir by acting on the viral load at the time of maximal reactivation and replication. This may also contribute to a lower rate of transmission from one individual to another by a reduction in oral shedding.[15] The TTH data may be evaluated in a different way by assigning patients with abortive episodes a healing time of zero, reasoning that blocked episodes do not contribute to the amount of time a patient has vesicles.[16] Using this analysis method, the TTH difference in this study increased from 0.3 to one day. Early dosing and high drug concentrations in saliva and mucosal tissue may modify the clinical course of disease by reducing the incidence of recurrence and delaying the onset of the next episode.

THINKING SHORT-TERM

In summary, treatment duration for HSV-1 infections has shortened as we have learned more about the disease pattern, site of replication, and time to maximal viral replication with respect to the prodromal symptoms that almost always accompany the onset of an episode. There are many good options for treating HSV. It seems putting the decision of when to treat in the hands of the patient might produce better outcomes. ∎

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