CLINICAL INSIGHTS

SPONSORED BY CIPHER PHARMACEUTICALS 2016, No. 1

Acyclovir Buccal Adhesive Tablet

Enhanced benefits from a new delivery system.



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It is estimated that herpes simplex virus-1 (HSV-1) infection affects 85 percent of the world's population. Many of these patients carry the virus asymptomatically, as only 40 percent of these patients manifest clinical infections.[1-3] Patients with frequent herpes labialis infections experience at least four episodes per year.[4,5] Early, effective treatments are important, as HSV outbreaks are highly stigmatized and affect quality of life.[6]

Once HSV infects a patient, it remains latent in the trigeminal ganglion and in the oral mucosa.[7] Viral replication becomes active at the onset of prodromal symptoms and peaks as the lesion develops. Transmission occurs after direct contact with lesional skin or mucous membranes or with oral secretions.[8,9] Based on this knowledge of viral replication rates and lesion progression, the recommendation for treatment is to provide a high concentration of medication as soon as a prodrome begins in the hopes of aborting the development of a clinical cold sore.[10]

Systemic antiviral medications have been the treatment of choice for patients with recurrent orolabial HSV. These include acyclovir, valacyclovir, and other related drugs. While oral administration can offer effective results, the drugs must undergo first-pass metabolism in the gut, followed by systemic distribution to the site of infection in the oral mucosa. After oral administration, acyclovir concentrations have been shown to be low within the labial mucosa and short lived, with a half-life of approximately 1 hour.[11-14] As the virus replicates in the basal layer of the oral mucosa, while systemic administration is effective, it does not optimize delivery of the drug to its target location.

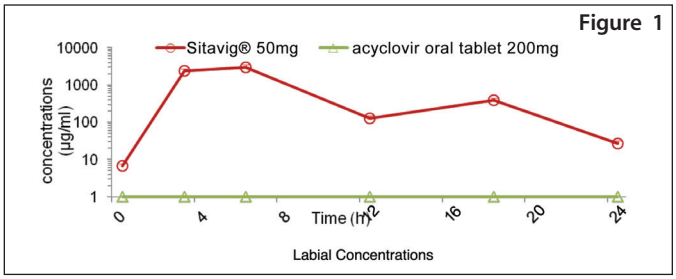
Advances in drug delivery technology have brought a new delivery system of acyclovir directly to the site of the infection. Sitavig® (Cipher Pharmaceuticals) is a 50mg acyclovir mucoadhesive buccal tablet, using Lauriad® technology that provides a sustained release of active drug within the oral cavity. The drug is designed to be applied to the gum in the canine fossa above the incisor tooth, where it stays in place and slowly dissolves over 12-14 hours releasing the drug directly into the oral cavity. In this way, drug levels are rapidly detectable in the saliva and oral mucosa within minutes and sustained for greater than 24 hours. Acyclovir concentrations were greater than 1000-fold higher than that achieved with a 200mg oral acyclovir tablet.[15]

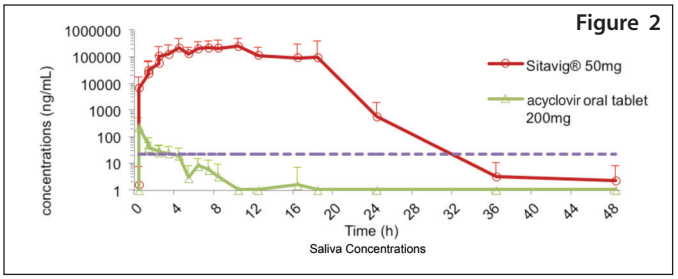
PHASE 3 CLINICAL TRIAL DATA

The acyclovir buccal tablet was evaluated in a multi-center, double-blind, placebo-controlled trial that enrolled 775 patients with recurrent herpes labialis. Patients were at least 18 years old and were required to have had a history of at least four clinical episodes of herpes labialis outbreaks over the preceding 12 months. Patients were randomized 1:1 to receive either 50mg acyclovir buccal tablet or placebo and instructed to apply the study medication within one hour of the onset of prodromal symptoms, before the development of any vesicles.[16]

The study's primary endpoint was the time to healing (TTH) of the clinical vesicular lesion, defined as complete resolution of the crusting. Secondary endpoints included duration of episode, the incidence and time to healing of abortive lesions (defined as outbreaks that did not progress past a papular stage and did not form vesicles), and incidence and TTH of secondary lesions. Time to cessation of symptoms was also captured—defined as the time it took for all symptoms to resolve. Finally, time to recurrence of the next herpes labialis outbreak was evaluated during a nine-month follow-up period.[16]

A total of 1,727 patients were enrolled in the study and randomized for treatment. Of those, 775 patients were treated; 378 in the active group and 397 in the placebo group. Baseline characteristics were well matched across patients in both treatment arms. Almost 68 percent of patients developed vesicular lesions, while slightly more than 31 percent experienced abortive episodes. A statistically higher percent of the patients in the placebo arm developed vesicular lesions versus those in the active arm, 70.6 percent vs 64.3 percent (P=0.042). Moreover, a greater number of patients in the active arm developed abortive episodes compared to placebo (relative rate of increase of 24.2 percent). The duration of episode was shorter in the active arm at 5.6 days vs. placebo at 6.4 days (P=0.003), and active patients had 33.7 percent fewer secondary lesions (P=0.037), which healed 2.1 days faster than placebo (P=0.068). Finally, the time to healing of the primary vesicular lesion was significantly quicker in the acyclovir buccal tablet group compared to the placebo group, seven versus 7.3 days, respectively (P=0.015), and when the abortive lesions were accounted for by setting their TTH to zero, the TTH was five





days vs six days (P=0.0017).[16]

Of the 775 patients treated, 537 entered into an observational period after their initial episode to monitor for lesion recurrence. There were statistically significantly fewer herpes labialis recurrences in patients who were treated with the acyclovir buccal tablet compared to those who received the placebo (P=0.027). Of those patients who received the active drug, 64.2 percent (149 of 267 patients) as opposed to 73.6 percent of patients on placebo (181 of 270 patients) developed a recurrence in the nine-month follow-up period. Besides a fewer number of recurrences, patients treated with the acyclovir buccal tablet also experienced a significantly longer time to recurrence, as compared to placebo (P=0.041). In the active arm, the median time to recurrence was 205 days, versus 165 days in the placebo arm.[16]

The drug was safe and well tolerated throughout the study. In the large majority of patients, the tablet adhered to the gum in the canine fossa for at least six hours. Adverse events were similar in both treatment arms, and there were no serious adverse events reported in the active treatment arm. The most common adverse events reported were headache and application site pain, which occurred similarly in both the active and placebo groups.[16]

DISCUSSION

While quick resolution of herpes labialis is important, prevention of lesion progression is perhaps even more a priority in patients with recurrent disease. Systemic antiviral medications are used as prophylaxis at the first prodromal symptom, but data on their use is sparse.[16,17] In this Phase 3 study evaluating the efficacy and safety of acyclovir buccal tablet, a high number of abortive lesions were reported, translating to fewer clinical vesicular outbreaks. Likely this effect is directly related to the method by which the drug is delivered to the site of infection, with rapid delivery of high concentrations of acyclovir to the oral mucosa with sustained levels over many hours.[15]

While aborting the progression of preclinical herpes labialis lesions is essential, primary prevention of recurrence is perhaps even more important in patients who suffer from recurrent outbreaks. In one study, continuous twice daily dosing of oral acyclovir was shown to suppress future outbreaks. After four months of 400mg acyclovir twice daily, the average duration before future outbreak was 118 days, as compared to 46 days in patients taking a placebo (P=0.05).[18] In the currently described study, a single dose of acyclovir buccal adhesive tablet reduced the herpes labialis recurrence risk by 22.7 percent during a nine-month follow-up period. The median time to recurrence was 224 days in patients who applied a single dose of the drug within one hour of initial prodromal symptoms.[16] This greater time to recurrence may be attributed to the high, continued dose of drug as a result of the being administered directly to the site of infection and thereby reducing the viral reservoir in the oral mucosa.[15]

While traditionally dosed oral antiviral medications have demonstrated efficacy in treating herpes labialis, advances in drug delivery have made an effective drug even more effective. By applying the drug within the oral mucosa with a buccal adhesive tablet, first pass metabolism from the gut is avoided, and high drug concentrations may be rapidly achieved at the site of infection. The drug has been shown to be both safe and effective in improving time to healing of clinical lesions. Moreover, when dosed within one hour of the first prodromal symptom it has been demonstrated to significantly block progression of lesions to a vesicular stage, and with even a single dose may lead to significantly fewer disease flares in the future. ■

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