Can We Change the Course of Herpes Simplex Labialis?

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In a recent publication of the Journal of the American Academy of Dermatology, researchers from Massachusetts General Hospital in Boston revealed that cold sores are one of the top two most stigmatized skin conditions.1 We as providers have a unique opportunity in the treatment of cold sores, as Bentley et al. said, “to restore social acceptance and self-esteem.”2

The Phase 3 pivotal LIP Trial demonstrated the unique clinical benefit of a novel formulation of an acyclovir buccal tablet 50mg, or ABT 50mg (Sitavig, Cipher Pharmaceuticals), for recurrent herpes simplex labialis in immunocompetent adults.3 Because of the mucosal delivery of ABT 50mg, rapid, markedly high, and sustained concentrations of acyclovir are delivered to the labial mucosa, the anatomic location where viral replication occurs in cold sores.4 In the pivotal trial, time to healing and duration of episode were improved; however, the statistically significant endpoints of increasing the time to recurrence and blocking the blister stage were clinical firsts and very promising.3 The ABT 50mg group had a mean improvement of 105 days free from cold sores over placebo, and 35 percent of lesions treated with ABT 50mg were blocked from reaching the blister stage (relative rate of increase of 24.2 percent over placebo).3 An exploration into how a targeted single dose of ABT 50mg can potentially increase time to recurrence and block the blister stage is warranted, and the scientific literature reveals possible mechanisms at work.

A REDUCTION IN VIRAL LOAD?

In regard to the increase in time to recurrence with ABT 50mg, noted dermatologist and virologist Stephen Tyring, MD, PhD said, “The reduction of subsequent (herpes) outbreaks is thought to be but not known to be due to the reduction of viral load.”5 Based on laboratory animal model studies, we know that the magnitude of the latent viral pool is strongly correlated to the frequency and severity of recurrence.6-9 Nancy Sawtell, PhD, virologist and HSV expert at the University of Cincinnati, as well as Yo Hoshino, MD, PhD and others, have published important and extensive findings on HSV-1 reactivation. Indeed, animals with a larger latent viral pool (as quantified by PCR of viral DNA) have a higher frequency of recurrence, and those with a smaller latent viral pool have a lower frequency of recurrence.6-9 It stands to reason that with a decrease in the frequency of recurrence of herpes labialis, the latent viral pool has likely been reduced.

LOCALLY IMMUNOMODULATORY?

The peripheral nerves in the mucosa terminate at the dermo-epidermal junction, and in infected persons, HSV-1 specific CD8+ T cells patrol the area to help prevent reactivation.9,10 The deleterious inflammatory host response contributes considerably to the time required for healing of herpes labialis lesions. Acyclovir has been shown to have an immunomodulatory effect.11,12 The duration of episode as well as time to cessation of symptoms in the LIP Trial were reduced in the ABT 50mg group, and the differences were statistically significant.3

RESERVOIRS AND LATENCY

While it was previously thought that HSV-1 lies exclusively in the trigeminal ganglia until a recurrence, Roizman and Whitley reported that there is a “…virtually continuous presence of viral DNA in mucosal tissues subject to periodic reactivation of HSV.”10 Animal studies have shown the ability of HSV-1 to maintain non-neuronal sites of latency in soft tissues.3,14 Furthermore, a UV-induced cold sore reactivation study by Dr. Spruance demonstrated a bimodal temporal reactivation.15 This bimodal distribution suggests that immediate lesions recurred due to a mucosal reservoir and that later lesions were delayed as a result of the time required for anterograde axonal transport of the virus from the trigeminal ganglia to the mucosal site of replication. Overall, HSV-1 is more ubiquitous than previously thought and likely has reservoirs not only in the trigeminal ganglia, but in the peripheral nerves and soft tissues as well. This presence, combined with viral replication occurring in the basal layer of the oral mucosa, suggests that obtaining targeted and high concentrations of antivirals in the oral mucosa is paramount in treating herpes labialis.

IMPORTANCE OF TARGETED DELIVERY

With relentless anti-viral bathing of the oral mucosa and intense inhibition of replication at the site of infection, possibly there is less viral progeny available for future recurrences. A Phase
1 pharmacokinetic/pharmacodynamic trial published last year showed ABT 50mg had rapid, high, and sustained saliva concentrations measured at 17,000-fold higher than the inhibitory concentration 50 (IC50). The saliva concentration was above IC50 for more than 32 hours. Labial tissue concentrations were also rapid, high, and sustained for more than 24 hours, long after the buccal tablet had fully dissolved (median time to dissolution, 14 hours) suggesting a depot of drug availability diffused in the oral cavity. HSV-1 takes about 14 hours for one round of replication in-vitro, suggesting that the pharmacokinetics of ABT 50mg closely match the pathophysiology of herpes labialis. Simultaneously, systemic drug exposure with ABT 50mg was limited. In contrast, oral antiviral therapy is usually in gram doses and is not without systemic considerations. Cases of acute nephrotoxicity and renal failure have been reported with oral antiviral therapy.

CHANGING THE COURSE OF COLD SORES
ABT 50mg is the first antiviral drug that with episodic treatment has demonstrated a reduction in the number of cold sore outbreaks. Additionally, it showed an increase in the number of lesions blocked from progressing to the blister stage. These clinical outcomes are particularly important for patients with cold sores, and demonstrate a change in the course of this most stigmatizing skin condition.

### RETROGRADE AXONAL TRANSPORT?
Upon primary infection of HSV-1 in herpetic simplex labialis, the virus (via the saliva) enters the basal layer of the oral mucosa where it replicates within the nucleus of the keratinocyte leading to lysis with vesicle formation and surrounding erythema. Through viral replication, the viral progeny are made available for release with vesicle formation and surrounding erythema.

### CASES OF ACUTE NephROTOXICITY AND RENAL FAILURE HAVE BEEN REPORTED WITH ORAL ANTIVIRAL THERAPY.

**Figure 1**

**Figure 2**

1. In the Phase 3 LIP Trial, secondary lesions were reduced by a relative rate of 33.7 percent lower than placebo, and healed 1.4 days faster, an effect of ABT 50mg that is anatomically distinct from the primary herpes labialis lesion.

**REFERENCE**