Decreased Labial Herpes Simplex Virus Outbreaks Following Botulinum Neurotoxin Type A Injection: A Case Report

Erin Gilbert MD PhD,[a] Jia Zhu PhD,[b] Tao Peng PhD,[b] and Nicole L. Ward PhD[c,d]

[a]Brooklyn, New York, NY

[b]Department of Laboratory Medicine, University of Washington and Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, WA

[c]Departments of Dermatology and Neurosciences, Case Western Reserve University, Cleveland, OH

[d]The Murdough Family Center for Psoriasis, University Hospitals Cleveland Medical Center, Cleveland, OH

ABSTRACT

Herpes Labialis results from reactivation of latent herpes simplex virus (HSV-1 or HSV-2) harbored in the trigeminal ganglion during times of psychological stress, cutaneous injury or photo exposure. Following reactivation, the virus is anterogradely transported through axonal termini to the skin where the virus is released and replicates causing a clinical outbreak. Botulinum neurotoxin A (BoNTA) is known to inhibit presynaptic neuropeptide and neurotransmitter release. Whether it has the capacity to interfere with viral shedding and delivery into the skin remains unclear. We were interested in determining whether BoNTA could serve as a potential therapeutic or prophylactic treatment approach for frequent and severe HSV recurrences. We describe a clinical case report in which a patient successfully maintained a sustained absence of HSV outbreaks in regions where BoNTA was intradermally administered. BoNTA may offer a novel therapeutic approach for preventing recurrent HSV disease.

J Drugs Dermatol. 2018;17(10):1127-1129.

CASE REPORT

A 33-year-old Caucasian female patient presented to the Dermatology clinic with a severe case of eczema herpeticum involving the face and dorsal medial hands complicated by impetigo. She had a longstanding history of atopic dermatitis and a 5-6-year history of monthly labial HSV outbreaks on the left upper lip. Although her atopic dermatitis had been controlled using topical steroids, she continued to experience frequent and regular HSV eruptions.

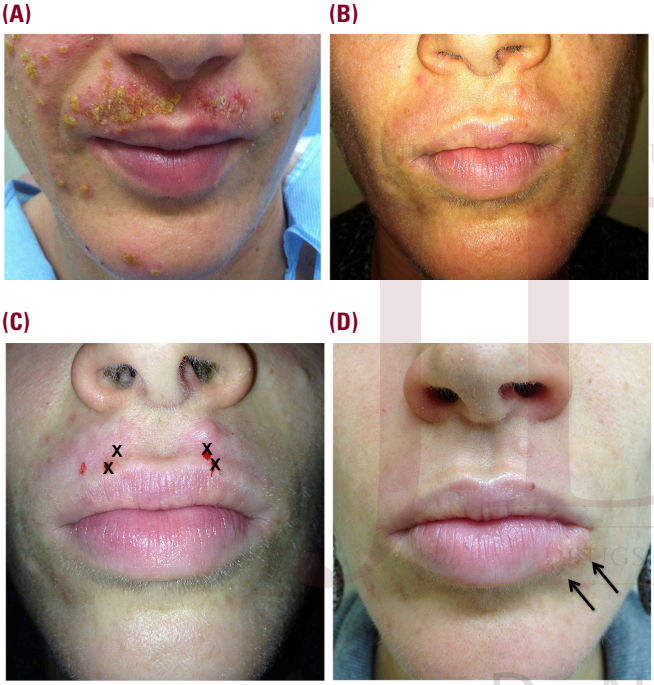
The patient was initially treated for her severe eczema herpeticum and impetigo (Figure 1A) with Keflex 500mg PO TID x 14 days, acyclovir 400mg PO x 7 days, and 2.0% mupirocin ointment topically TID x 10 days. Eight days following initial onset of treatment, this outbreak resolved. The patient was allowed to heal for an additional 7 weeks (Figure 1B) at which time we initiated the off-label use of BoNTA as a prophylactic approach to prevent future HSV outbreaks. The initial treatment with BoNTA involved intradermal injections of 1 unit each of onabotulinumtoxinA (BOTOX) injected at 4 sites on the upper cutaneous lip (Figure 1C), spaced approximately 1cm apart. No adverse effects were observed at the time of injection or one week following. However, a new HSV lesion appeared in the upper right perinasal region, 4 weeks later (not shown). No new lesions appeared for the next 10 weeks. A new outbreak of attenuated eczema herpeticum appeared 8 weeks following the initial BoNTA injection, however the areas of skin injected with BoNTA (peri-oral) were spared (not shown).

The patient presented with a new HSV outbreak 4 months after the initial BoNTA injections and it was determined that she be re-treated. The patient was initially treated with standard of care, acyclovir 400mg PO 5x daily for 5 days. One week after completing acyclovir treatment she was then reinjected with 15 units of abobotulinumtoxinA (Dysport). Again, the BoNTA treatment prevented HSV flares at the site of the original outbreaks, however three months later she developed two flares of HSV on the left lower lip (Figure 1D), where she had not been treated. The fulminant upper lip outbreaks were eradicated with repeated BoNTA dosing at four-month intervals for 19 months.

DISCUSSION

According to the World Health Organization, 3.7 billion people under the age of 50 are infected with HSV-1.[1] HSV-1 is thought to cause roughly 80% of orolabial cases, and HSV-2 the remaining 20%.[2] HSV outbreaks occur when a latent virus becomes reactivated and is delivered to the skin via sensory nerves, and the reactivated virus replicates productively in the skin and forms an ulcerative lesion. HSV reactivation from latency stage can be triggered by various stimuli, including sickness and fever, trauma, emotional stress, sunlight and

FIGURE 1. (A) Representative image of the peri-oral region of the patient when she presented with severe eczema herpeticum and impetigo. (B) Clearance of the skin 7 weeks following initial treatment with Keflex, acyclovir and 2.0% mupirocin ointment. (C) Sites in the perioral region where 1 unit each of onabotulinumtoxinA (BOTOX) was intradermally injected (1 unit/X). (D) Two HSV flares on the left lower lip (arrows) developed in areas where BoNT had not been injected, while outbreaks on the fulminant upper lip were eliminated.



possibly even hormonal changes related to menstruation.[1] Currently, prevention of outbreaks of HSV is limited to oral antiviral therapy. However, targeting the delivery of activated virus from the nerve to the skin has not been examined.

We have previously demonstrated the efficacy of BoNTA in improving psoriasiform skin inflammation in the KC-Tie2 mouse model of psoriasis[3] and have attributed the improvement to blockade of sensory nerve derived Substance P and CGRP. These preclinical findings were successfully translated to the treatment of a recalcitrant buttock psoriasis plaque in a patient where intradermal injection of AbobotulinumtoxinA (Dysport) successfully resolved the plaque.[4] Interestingly, when this patient's psoriasis recurred 8 months after treatment, an HSV outbreak was noted on the contralateral buttock.

In the current case, BoNTA injection prevented labial HSV outbreaks at the site of treatment. However, outbreaks did occur at untreated sites, suggesting that the prophylactic effect by BoNTA was specific to the region directly around the injection sites.

Additional off-label uses of BoNTA include treatment for non-histaminergic itch,[5-7] inverse psoriasis of the axilla and inframammary regions,[8,9] and with doses of toxin between 50-100 total units/site. Here, we report prophylactic improvement in HSV outbreaks in the perioral region following intradermal treatment with 4 units of onabotulinumtoxinA (BOTOX®) or 15 units of abobotulinumtoxinA (Dysport®). At presentation the patient had monthly herpes labialis outbreaks for 5-6 years, and prophylactic BoNTA suppressed fulminant outbreaks across a period of 1.7 years. The timing of HSV relapse was aligned with the timing of glabellar line improvement and reappearance following intramuscular injection of BoNTA. To our knowledge, this is the first report of preventative efficacy in an HSV patient and identifies a novel use for BoNTA in prophylaxing against herpes labialis outbreaks.

The effectiveness of BoNTA in preventing HSV labialis outbreaks highlights the active role that peripheral nerve networks play in influencing the frequency and severity of HSV reactivation. The dynamic interactions between sensory nerve termini and infected cell targets have been investigated in biopsy tissue during natural HSV-2 reactivation in humans.[10]

In HSV-2 affected skin, the axonal nerve endings for releasing reactivated HSV viral particles are shown to sprout upward and form direct contacts with basal keratinocytes, the peripheral targets of HSV. These close interactions between nerve endings and basal keratinocytes implicate that the direct delivery of HSV viral particles to peripheral target cells might be required to achieve optimal and productive viral replication in the periphery. Additionally, HSV infection of keratinocytes has recently been shown to actively modify cutaneous nerve networks, promoting directional nerve fiber growth and branching toward the basal keratinocytes in local tissue.[11]

This modification of the peripheral nerve networks observed in vivo in humans involves the production of IL17c by keratinocytes upon HSV infection and the functional interactions between IL17c and its receptor IL17RA/RE expressed on the nerve termini. Higher nerve fiber ending density has been associated with HSV affected skin as compared to uninvolved normal control skin. Together, these findings emphasize that the skin-innervating nerve networks, and their active communication with peripheral cell targets, shape the pathogenesis of HSV diseases in humans.

The mechanisms by which BoNTA prevents HSV infection remain unclear. We hypothesize that similar mechanism of BoNTA-mediated blockade of synaptic vesicle release might occur. Specifically, that vesicles carrying HSV are prevented from being released into the cutaneous region innervated by nerve endings. The critical step during HSV reactivation is to release the reactivated virus particles from axon terminals to infect peripheral target cells, the basal keratinocytes. This egress step has been associated with axon varicosities.[12,13]

HSV reactivation is generally thought to go through small unmyelinated nerve fibers near the dermal-epidermal junction of skin, such as C-type fibers. BoNTA is known to cleave snap25, a presynaptic membrane protein that regulates neurotransmitter release, thus, it is likely that BoNTA inhibits HSV reactivation by inhibiting HSV egress from axons to infect keratinocytes. It is also tempting to think that BoNTA could inhibit virus replication in epidermal keratinocytes and DRG sensory neurons. How BoNTA affects HSV latency and reactivation in sensory neurons, viral axonal transportation and its accumulation at the varicosities of nerve terminals, warrants further investigation. We are currently exploring these questions in preclinical models as well as in human subjects.

The off-label use of BoNTA in other non-dermatological areas, including the fields of neurology, pain management and urology is increasing as the utility of BoNTA continues to grow. Within dermatology, FDA-approved uses of BoNTA include treatment of glabellar lines, crow's feet and hyperhidrosis and several recent reports show the success utilization of BonTA for the off-label treatment of medical dermatology conditions, including recalcitrant itch,[5-7] with interest growing in its potential efficacy for treating skin conditions including rosacea and acne, as well as other neurogenic inflammation-driven cutaneous inflammatory conditions.

In conclusion, we show here a significant decrease in the number of reported outbreaks of cutaneous HSV following prophylactic BoNTA treatment. We propose the use of BoNTA for treating recurrent HSV outbreaks is most suited for patients whose HSV is first driven into remission with standard-of-care treatment, acyclovir; followed by prophylactic administration of BoNTA into the skin regions most heavily affected by virus outbreak. Our report suggests that BoNTA may offer an affordable, durable, low maintenance approach to treating significant recurrent HSV outbreaks.

DISCLOSURE

Dr. Gilbert has served as a paid consultant for Merz, Allergan, Medicis, and Galderma; Dr. Ward has served as a paid consultant or speaker for Allergan and AbbVie, has had a research agreement with Allergan for unrelated studies, and receives research materials from Eli Lilly and Amgen.

REFERENCES

1. Knipe, D. & Howley, P. *Fields Virology 6th edition*, (2015).
2. Xu, F.,et al. Seroprevalence and coinfection with herpes simplex virus type 1 and type 2 in the United States, 1988-1994. *J Infect Dis.* 185:019-1024 (2002).
3. Ward, N.L., et al. Botulinum neurotoxin A decreases infiltrating cutaneous lymphocytes and improves acanthosis in the KC-Tie2 mouse model. *J Invest Dermatol* 132:1927-1930 (2012).
4. Gilbert, E. & Ward, N.L. Efficacy of botulinum neurotoxin type A for treating recalcitrant plaque psoriasis. *J Drugs Dermatol* 13:1407-1408 (2014).
5. Akhtar, N. & Brooks, P. The use of botulinum toxin in the management of burns itching: Preliminary results. *Burns* 38:1119-1123 (2012).
6. Salardini, A., Richardson, D. & Jabbari, B. Relief of intractable pruritus after administration of botulinum toxin A (botox): a case report. *Clin Neuropharmacol* 31:303-306 (2008).
7. Kavanagh, G.M. and Tidman, M.J. Botulinum A toxin and brachioradial pruritus. *Br J Dermatol* 166:1147 (2012).
8. Zanchi, M., et al. Botulinum toxin type-A for the treatment of inverse psoriasis. *JEADV* 22:431-436 (2008).
9. Saber, M., Brassard, D. & Benohanian, A. Inverse psoriasis and hyperhidrosis of the axillae responding to botulinum toxin type A. *Arch Dermatol* 147:629-630 (2011).
10. Zhu, J., et al. Virus-specific CD8+ T cells accumulate near sensory nerve endings in genital skin during subclinical HSV-2 reactivation. *J Exp Med* 204:595-603 (2007).
11. Peng, T., et al. Keratinocytes produce IL-17c to protect peripheral nervous systems during human HSV-2 reactivation. *J Ex Med* 214:2315-2329 (2017).
12. Diefenbach, R.J., Miranda-Saksena, M., Douglas, M.W. & Cunningham, A.L. Transport and egress of herpes simplex virus in neurons. *Rev Med Virol* 18:35-51 (2008).
13. Kramer, T. & Enquist, L.W. Directional spread of alphaherpesviruses in the nervous system. *Viruses* 5:678-707 (2013).

AUTHOR CORRESPONDENCE

Nicole L. Ward PhD or Erin Gilbert MD PhD

E-mail:..... nicole.ward@case.edu or doctorgilbert@gmail.com