

Phototherapy in the Treatment of Cutaneous Herpesvirus Manifestations

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There is a considerable need for effective and safe treatment of cutaneous herpesvirus lesions. Current common approaches are limited to expensive or multidose oral pills. This systematic review of evidence-based approaches to phototherapy for the various manifestations of the herpesvirus discusses original publications of controlled clinical trials and case reports that were identified through searches in PubMed, MEDLINE, and Ovid. Interventions included photodynamic therapy (PDT), UV light, and near-infrared lasers. Nearly all studies (10 of 11) saw reduction of most or all lesions and extended time before reactivation of the virus. Side effects often were minimal to nonexistent, usually mild erythema at sites of phototreatment. Serious side effects included first-degree burns and linear IgA dermatosis, which were not common. Evidence from the reviewed literature indicates that short-term efficacy from treatment with phototherapy is the most likely outcome. However, long-term effects and follow-up of this treatment modality are lacking but appear promising. We recommend future studies to include more patients, determine the most effective type of phototherapy, and assess long-term follow-up. Furthermore, light-based therapies can be considered a reasonable alternative in situations that preclude traditional drug-based therapies.

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Herpesviridae is a large family of linear, double-stranded DNA viruses characterized by their ability to remain latent and reoccur after treatment of the primary infection.¹ The types of viruses with cutaneous manifestations reviewed in this article are the herpes simplex virus (HSV)(herpes simplex virus type 1, herpes simplex virus type 2), varicella-zoster virus (VZV), human herpesvirus 7 (HHV-7), and Kaposi sarcoma (KS). Patients infected with the virus experience physical pain as well as psychological distress from the inflammatory reaction elicited by the immune system.

As one of the most common malignancies seen in AIDS patients, human herpesvirus 8–induced cutaneous KS is another visual manifestation that adds stress to a patient who is already dealing with the prognosis of AIDS. Exploration of therapies that reduce the patient’s infectious status as well as physical and emotional distress is therefore paramount, which is especially true in our current environment of prevalent zoster reactivation as well as HSV and other herpesviruses.² Current treatment of most herpes infections consists of inhibiting viral replication using nucleoside analogues such as acyclovir, famciclovir, and valacyclovir. Local treatments of KS lesions include radiation therapy, alitretinoin gel, vinblastine, and imiquimod cream.³⁻⁵ There are currently no in vivo studies that show the effectiveness of pharmacotherapy against HHV-7.⁶ These treatments have several limitations such as the requirement of regular oral medication intake, which can be difficult for some patient groups such as children; maintenance of patient compliance with oral regimens; and high cost of antiviral treatment. Additionally, current treatment does not cure the disease or prevent future recurrences.

Another approach to the treatment of the herpesvirus is to enhance the ability of the immune system to respond to and suppress the virus. This method would provide more of a lasting effect in the reduction of outbreaks and recurrences. Many of the light-based therapies reviewed here seek to stimulate

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the immune system through the activation of CD8 cells, release of cytokines, or induction of apoptosis and necrosis.⁷ Anecdotally, we have noted fewer herpetic ulcers in patients undergoing certain light therapies on a long-term basis, which seems to be particularly common with low-grade long-term treatments as opposed to short-term high-stress therapies such as laser rejuvenation. Furthermore, the atypical anti-infective uses of light were previously reviewed.⁸ This modality also is clinic based and does not require a patient to adhere to a treatment regimen at home.

The use of light as a treatment of viral infections has been a modality that has existed and has been used for decades. Studies published on the use of light-based energy treatment of herpes show that it is an effective alternative to pharmacotherapy. However, articles that focus on treatment of a cutaneous manifestation of Herpesviridae are not prolific. Study populations are not large and vary in size and type, ranging from randomized controlled trials to case reports on a single patient. The focus of this evidence-based review article is to evaluate these studies and encourage others to explore this treatment method.

Methods

Original publications were identified through literature searches in PubMed, MEDLINE, and Ovid. The searches were limited to English-language publications within the last 20 years. The following search terms were used: (1) *phototherapy*; (2) *photodynamic therapy*; (3) *photochemotherapy*; (4) *laser*; (5) *magnetic laser*; (6) *light*; (7) *red light*; (8) *blue light*; (9) *intense pulsed light*; (10) *pulsed dye laser*; (11) *tungsten lamp*; (12) *halide*; (13) *herpes*; (14) *Epstein-Barr virus*; (15) *cytomegalovirus*; (16) *varicella zoster*; (17) *exanthema subitum*; (18) *roseola infantum*; (19) *sixth disease*; (20) *Kaposi sarcoma*; and (21) *HHV-7*.

Subsequently, searches of terms 1 through 12 were combined with terms 13 through 21. Evaluation of articles included clinical trials and case reports with full-text articles involving the use of a light source to treat a cutaneous herpesvirus manifestation, herpes-associated side effects of light therapy, and basic science articles that involved mechanisms of viral killing with light. Finally, an analysis was performed to grade the level of evidence using the guidelines of the 3-letter grading system implemented by groups such as the American Academy of Family Physicians and UpToDate (grade A, high; grade B, moderate; grade C, low).

Results

A total of 11 clinical trial and case reports were identified as using a type of phototherapy for

the treatment of a cutaneous manifestation of Herpesviridae,^{7,9-18} involving a total of 267 patients. The results of our search are summarized in Table 1.

Herpes Simplex Virus—Four studies showed that symptomatic relief of genital and oral herpes labialis could be attained using phototherapy.^{7,9-11} Schindl and Neumann¹¹ evaluated the effect of low-intensity laser on recurrent perioral HSV infections with a randomized, double-blind, placebo-controlled study. The study population was split into a laser group and placebo group (n=25 each), with current antiviral treatment, immunosuppressant therapy, or human immunodeficiency virus infection as exclusion criteria. The protocol for the laser group consisted of irradiations of 10 minutes per 1 cm² at intensity of 80 mW/cm² with a dose of 48 J/cm² once daily for 2 weeks at the site of the original chronic herpes infection. The placebo irradiation was performed in the same manner, but the laser was not turned on. The results showed that the median recurrence-free interval in the laser group was 37.5 weeks in contrast to 3 weeks in the placebo group (P<.0001). No side effects were noted.¹¹

Dougal and Kelly⁹ sought the wavelength of light that would be the most effective for tissue penetration. They reasoned that tissue penetration would most likely be influenced by water. Examination of the transmission spectrum of water demonstrated a peak of transmission of light with a wavelength of 1072 nm. They recruited 60 patients for a randomized, prospective, double-blind study comparing the interventions of a single 5-minute application with optical power between 5 to 10 mW/cm² versus topical acyclovir applied 5 times daily until the cold sore was reported cured. Results showed that the active light group reported cold sore cures in a mean (standard deviation) of 4.3 (1.8) days versus 8.5 (3.0) days for topical acyclovir 5 times daily (P<.0001). No side effects were reported.⁹

Hargate¹⁰ used 1072-nm active near-infrared light to treat herpes labialis of the lips. Volunteers in a randomized double-blind study were exposed to 3-minute treatment intervals 3 times daily for 2 days of either 1072-nm light pulsed at 600 Hz and a pulse width of 300 milliseconds or placebo device with no light. The device showed a 33% reduction in healing time (mean [standard deviation] of 6.3 [2.99] days vs 9.4 [4.58] days; P=.048). No side effects were noted and no long-term effects were mentioned.¹⁰

Martin and Stoneburner⁷ used photodynamic therapy (PDT), a treatment modality that combines a photosensitizer with irradiation by light to exert its effects. The study applied chlorinated neutral red to the intervention group (n=16) and red food coloring

Table 1.

Studies on Phototherapy Treatment of Herpesviruses

Reference	Herpes Manifestation	Evidence Level ^a and Type of Study	Light Treatment	Settings and Protocol	Results and Significance
Dougal and Kelly ⁹	Herpes labialis	Evidence level A; randomized, prospective, double-blind study (N=60)	1072-nm narrow wave band light	Single 5-minute application with optical power (5–10 mW/cm ²) vs topical acyclovir applied 5 times daily	Active light group reported cold sore cures in a mean (SD) of 4.3 (1.8) days vs 8.5 (3.0) days for topical acyclovir 5 times daily (<i>P</i> ≤.0001)
Hargate ¹⁰	Herpes labialis	Evidence level A; randomized double-blind study (N=32)	1072-nm active near-infrared light	3-minute treatment intervals 3 times daily for 2 days pulsed at 600 Hz and a pulse width of 300 milliseconds vs placebo	Reduced healing time by 33%: 6.3 days in the active group vs 9.4 days in the placebo group (<i>P</i> = .048)
Schindl and Neumann ¹¹	HSV perioral lesions	Evidence level A; randomized, double-blind, placebo-controlled study (N=50)	Low-intensity laser (690-nm continuous-wave diode laser)	Irradiations of 10 minutes per 1 cm ² at intensity of 80 mW/cm ² with a dose of 48 J/cm ² once daily for 2 weeks at the site of the original chronic herpes infection	Median recurrence-free interval in the laser group was 37.5 weeks vs 3 weeks in the placebo group (<i>P</i> ≤.0001)
Martin and Stoneburner ⁷	HSV, oral and genital; VZV shingles	Evidence level B; multiphasic, comparison to control group (N=27)	UVA (exposed to chlorinated neutral red)	Lesion cleaned prior to application of neutral red or placebo red food coloring; then, irradiation by UVA1 (365 nm) emission from Wood or Burton lamp	At 24 hours, all treated herpes lesions appeared inactive with normal skin growing over the remaining crusted area
He et al ¹²	VZV	Evidence level B; case report (N=1)	UV-mixed wavelength	Oral acyclovir and vitamins for 1 week and received local irradiation with UV light ^b	Localized linear IgA dermatosis induced by UV light treatment

Reference	Herpes Manifestation	Evidence Level ^a and Type of Study	Light Treatment	Settings and Protocol	Results and Significance
Jalali et al ¹³	VZV, postherpetic neuralgia	Evidence level B; multiphasic, comparison to control group (N=25 for phase 1)	UVB	Prevention group: oral acyclovir (800 mg 5 times daily for 10 days) plus 3 UVB treatments weekly for 15 sessions or until resolution of symptoms (UVB dose started with 20 mJ/cm ² and gradually increased by 10 mJ/cm ² each session to a maximum dose of 100 mJ/cm ²); control group: administration of oral acyclovir alone	Cessation of pain at 1- and 3-month intervals: prevention group (n=12), 58.33% and 83.33%, respectively; control group (n=13), 38.46% and 53.85%, respectively (P≤.05)
Yaksich et al ¹⁴	VZV, postherpetic neuralgia	Evidence level B; clinical trial (N=25)	Low-energy laser therapy	2 individual units used separately: first unit emitted light at 820 nm with a continuous output of 40 mW; second unit emitted 904 nm with a pulse frequency of 5000 per second and an output of 5 mW	56% remarkable improvement based on criteria that good improvement was defined as resolution of hyperaesthetic pain
de Vries et al ¹⁵	HHV-7	Evidence level B; prospective nonrandomized (N= 18; only 1 patient received light treatment)	Psoralen plus UVA	96 treatments over 6 months	1 patient saw remission and a marked decrease of HHV-7–positive epidermal and dermal cells from 22.3 to 2.3 cells/mm ² , respectively, and from 39 to 5.9 cells/mm ² , respectively

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Table 1. (continued)

Reference	Herpes Manifestation	Evidence Level ^a and Type of Study	Light Treatment	Settings and Protocol	Results and Significance
Abels et al ¹⁶	KS	Evidence level B; pilot study (N=3)	Diode laser and indocyanine green (IV)	IV injection of indocyanine green (2–4 mg/kg body weight) within 50 minutes before light treatment; 805-nm diode laser delivered 100 J/cm ² and 0.5–5 W/cm ² of light	After a second course of treatment, 16 of 57 KS lesions achieved complete remission
Bernstein et al ¹⁷	KS	Evidence level B; clinical trial (pathologists blinded to samples) (N=25)	PDT (635-nm argon laser and porfimer sodium IV)	IV injection of porfimer sodium (1.0 mg/kg body weight) 48 hours before light treatment; argon laser delivered through a 400- or 600- μ m single-quartz filter produced a homogenous circular pattern; escalating doses of light (100–400 J/cm ²) were delivered at 150 mW/cm ² for 11.1–44.4 minutes; some larger lesions required more than 1 treatment over a period of a few months	32.5% of lesions had complete clinical response, 63.3% had partial clinical response, and treatment failed in 4.2% ($P \leq 0.0001$)
Tardivo et al ¹⁸	KS	Evidence level B; case report (N=1)	PDT (argon laser, 100 mW/cm ²)	(1) Obtain photograph of lesion; (2) inject mixture MB 2%, TB 2%, and lidocaine 2% (<5 mL) until lesion became dark blue; (3) laser applied with a total dose of 18 J/cm ² ; (4) new photographs taken 7 days after treatment	Lesions were visually reduced after treatment

Abbreviations: SD, standard deviation; HSV, herpes simplex virus; VZV, varicella-zoster virus; HHV-7, human herpesvirus 7; KS, Kaposi sarcoma; IV, intravenous; PDT, photodynamic therapy; MB, methylene blue; TB, toluidine blue.

^aEvidence levels: grade A, high; grade B, moderate; grade C, low.

^bNo light settings, fluency, or protocol available from article.

on the placebo group (n=11) for both oral and genital herpes lesions. Both groups were then irradiated with a single treatment of UVA1 light at a maximum of 365 nm from a Wood or Burton lamp that did not exceed 30 minutes of exposure. At 24 hours, all of the HSV skin lesions treated with neutral red followed by UVA1 light appeared inactive with normal skin growing over the remaining crusted area. The placebo group showed no response. A tingling sensation was noted in areas of neutral red irradiated by UVA1. No *P* value or long-term effects were noted.⁷

Varicella-Zoster Virus—Several articles explored light as treatment in the reactivation of the varicella-zoster virus/shingles and its sequelae, postherpetic neuralgia.¹²⁻¹⁴ Martin and Stoneburner⁷ also examined the effects of its regimen on patients with VZV shingles. One group received chlorinated neutral red (n=4) and 1 group received red food coloring placebo (n=2) followed by UVA1 light and met with the same results seen in HSV skin lesions; within 24 hours, all participants responded to the treatment with reduced pain and increased signs of healing. The publication did not mention a *P* value for its results, side effects in addition to tingling, or relief of postherpetic neuralgia or long-term effects of the treatment.⁷

Jalali et al¹³ sought a novel approach to the treatment of postherpetic neuralgia because the current treatment of established postherpetic neuralgia is difficult and often disappointing, especially for elderly patients. The prevention group (n=12) received oral acyclovir 800 mg 5 times daily for 10 days plus broadband UVB to the affected dermatomes, starting with 20 mJ/cm² and gradually increasing the dose by 10 mJ/cm² each session to a maximum dose of 100 mJ/cm². Treatment sessions were repeated 3 times weekly until pain relief or to a maximum of 15 sessions. The control group (n=13) only received oral acyclovir with the same dose as the prevention group. In the case of frank erythema or burning, treatment was withheld until the erythema faded. Two patients developed a first-degree burn that resolved with cessation of phototherapy. No other adverse events were reported. Results showed a cessation of pain in 58.33% and 83.33% at 1- and 3-month intervals, respectively, following treatment in the prevention group, which is in contrast to the 38.46% and 53.85% level of pain reduction of the control group, respectively (*P*≤.05). The prevention group also had a lower verbal response score for the severity of pain at 3 months compared with the control group (2.50 vs 3.28).¹³

Human Herpesvirus 7—Human herpesviruses are at times associated with other diseases. For example, Epstein-Barr virus has been associated

with Burkitt lymphoma or human herpesvirus 6 with drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome.¹⁹ The de Vries et al¹⁵ study found that lichen planus remission is associated with a decrease of HHV-7 protein expression in plasmacytoid dendritic cells. In this study, various modes of treatment were used to induce remission of lichen planus, with 1 modality being the use of psoralen as a photosensitizer and UVA phototherapy to treat 1 patient in the trial. In this patient with a lower leg lesion, the number of HHV-7-positive epidermal and dermal cells pretreatment was 22.3 and 39 cells/mm², respectively. After remission of the lichen planus lesion, the number of HHV-7-infected cells was reduced to 2.3 and 5.9 cells/mm², respectively. No *P* value was available for the treatment of interest to this article nor was there any discussion of side effects.¹⁵

Kaposi Sarcoma—The modality for treating human herpesvirus 8-related KS skin manifestations reviewed here all involve the use of PDT with varying photosensitizers and light sources. In a clinical trial, Bernstein et al¹⁷ treated 348 lesions in 25 patients by administering 1.0 mg/kg body weight of porfimer sodium, a drug that preferentially accumulates in tumor tissue, intravenously 48 hours prior to light treatment. The light was from an argon laser (through a 400- or 600- μ m single-quartz filter) pumping a 595-nm pulsed dye laser. Escalating surface treatment of light doses of 100 to 400 J/cm² were delivered at 150 mW/cm² for 11.1 to 44.4 minutes. Side effects in 27% of the patients included cutaneous phototoxicity reactions,¹⁷ similar to the rate of noncompliance (patients were advised to avoid bright light and sunlight without protection for 4 weeks) in other porfimer sodium studies.²⁰ The sunburn-type reaction of slight erythema to slight edema occurred only on sun-exposed surfaces, most frequently the face and neck.¹⁷ However, the reactions subsided within 72 hours and no other phototoxicity was noted. The results from 289 evaluable lesions showed a 32.5% complete clinical response, 63.3% partial clinical response, and 4.2% clinical failure rate (*P*≤.0001). No long-term follow-up was mentioned.¹⁷

Abels et al¹⁶ observed that as a photosensitizer, indocyanine green (ICG) allowed for deeper tissue penetration of near-infrared light compared to other photosensitizers. A pilot study was conducted with 3 KS patients. Each was given an intravenous injection of ICG dosed at 2 to 4 mg/kg body weight (applied in 2 doses) within 50 minutes before light treatment. An 805-nm diode laser delivered 100 J/cm² and 0.5 to 5 W/cm² of light. Complete remission of KS was achieved in 16 of 57 lesions when irradiated 1 to 30 minutes after injection of the second dose

of ICG. Biopsies (n=3) showed complete remission after 4 weeks. No systemic side effects were observed.¹⁶

Tardivo et al¹⁸ locally and superficially injected a mixture of methylene blue 2%, toluidine blue 2%, and lidocaine 2% at lesion sites. The injected lesions were then irradiated with an argon pumped dye laser 100 mW/cm² or with a noncoherent light source. The total laser dose applied was 18 J/cm². This protocol was carried out every week for 4 months and then every 2 weeks for 6 months in the same site or another site according to evaluation of the lesion. The average number of treatments was 5 per site. The result was complete remission with encouraging cosmetic results as illustrated by photographs within the article.¹⁸

Comment

A summary of the mechanisms of phototherapy and its cellular and viral effects are available in Table 2.

There are several hypothesized mechanisms for the induction of the immune system by light-based therapy.²⁶ Near-infrared wavelengths such as 1072-nm light improves lymphocyte viability in culture but also conveys a level of cytoprotection against the toxic effects of UV light, which is a known precipitant of cold sores.²⁷⁻²⁹ It has been shown that irradiation of lymphocytes with low-level lasers leads to an increase in their adenosine triphosphate levels, which is due to photons accelerating the redox reactions within the electron-transport chain.²¹

Other light modalities such as UVB operate via other mechanisms. UVB may be successful in reducing the effect of postherpetic neuralgia by suppressing the immune system. One of the probable targets is the Langerhans cell (LC) network.¹³ UVB light suppresses the antigen presentation by LC, causing depletion of LCs in the epidermis and downregulating the expression of class II major histocompatibility complex and intercellular adhesion molecule 1 on the surface of LCs.³⁰ Additionally, UVB modifies the T-cell response to persistent VZV particles in nerve fibers. The inflammatory response by the body is primarily T_H1 type (helper T cells) with the release of IFN-γ and IL-2,³¹ whereas UVB induces a shift from a T_H1 to a T_H2 response by inducing the release of IL-10, an immunosuppressive cytokine. IL-10 interferes with the signal transduction pathway of IL-2 and IFN-γ. Pain relief in postherpetic neuralgia after irradiation by UVB also may be the result of structural changes such as reduced epidermal nerve fibers seen on electron microscopy.³²

With the use of photosensitizers in PDT such as neutral red, methylene blue, toluidine blue, porfimer sodium, indocyanine green, or 5-aminolevulinic acid combined with irradiation by a

Table 2.

The Effects of Light Therapy on Cells and Herpesviruses

Treatment Modality	Cellular and Viral Effects
Near-infrared light	Enhances immune response and lymphocyte proliferation; ATP levels are increased in irradiated lymphocytes through photons accelerating the redox reactions within the electron-transport chain ^{11,21}
UVB light	Induces release of IL-10 and inhibits signal transduction pathway of IL-2 and IFN-γ, shifting T _H 1 (helper T cells) immune response to T _H 2 mediated ¹³
Photodynamic therapy	
5-ALA plus 400–700-nm light	Damages herpes simplex virus type 1, likely by peroxidation postabsorption in the late phase of viral cycle, inhibiting viral neoformation spread cell to cell ²²
Indocyanine green plus diode laser	Cell death induced by photooxidation and formation of reactive oxygen species; used as focal treatment ²³
Methylene blue plus light	Binds viral DNA and photoactivated to create singlet oxygen; also increases expression of IL-6, thereby stimulating cytotoxic T cells that destroy infected cells ^{18,24,25}

Abbreviations: ATP, adenosine triphosphate; ALA, 5-aminolevulinic acid.

light source, the primary mechanism is the generation of reactive species that cause death in living cells and microorganisms including viruses.³³ However, PDT also has been shown to be immunomodulatory in its

stimulation of the immune system by enhancing the role of CD8⁺ T cells³⁴ and increased IL-6 expression, which increases the activity of cytotoxic T cells.^{35,36}

In general, side effects were mild to nonexistent in lieu of some extreme cases that saw first-degree burns from phototherapy and 1 case report of linear IgA dermatosis induced by UV light.¹² During our literature search for phototherapeutic modalities to treat herpes manifestations, we found several articles that saw the reactivation of HSV as a side effect in itself. A retrospective study reviewing the use of UVB to treat various skin conditions in children such as psoriasis and atopic eczema saw 2 cases of HSV and 1 case of VZV reactivation after treatment.³⁷ Another study used UVB-emitting fluorescent lamps to induce HSV reactivation.³⁸ Finally, a case report discussed the rare event of HSV reactivation after pulsed dye laser treatment of a girl with Sturge-Weber syndrome.³⁹

The results of the publications reviewed in this article show that cutaneous herpesvirus manifestations may be treated with nonpharmaceutical techniques. The advantages to using phototherapy are the reduction in systemic side effects one might see with antivirals, radiation therapy, or vinblastine, as well as the decreased chance of the herpesvirus developing a resistance to the treatment and the potential decrease in treatment time to as little as 1 day. Often times, there also is the added benefit of reduction in treatment cost.

However, there is a need for larger, more comprehensive studies measuring long-term effects to determine the best combination of light frequency and/or photosensitizing agent. The wide range of light modalities reviewed here were not the sole modes of therapy in some studies. Given the varied methods, the data do not lend themselves well to meta-analysis. Future studies also should focus on achieving a greater specificity for herpes viral particles, both at the site of the lesion and systemically to prevent future reactivation. A delivery method of photosensitizing agents that is more specific for herpesvirus lesions using nanocarriers may increase the effectiveness of the phototherapy.^{40,41} The use of nanoparticles such as buckyballs that bind viral structures and induce reactive oxygen species in themselves also may be a possibility. One study inactivated enveloped viruses from 2 different families—the Semliki Forest virus (Togaviridae) and vesicular stomatitis virus (Rhabdoviridae)—with visible light and water-soluble buckminsterfullerene (C₆₀).⁴² There is a need to further expand research and develop more definitive and effective phototherapies for the various cutaneous manifestations of the herpesvirus.

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