Photodynamic Therapy with Red Light and 5-Aminolaevulinic Acid for Herpes Simplex Recurrence: Preliminary Results

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Herpes simplex viruses, HSV-1 and HSV-2, are the most common cause of mucocutaneous infection with a chronic and recurrent course. Approximately 20% of people infected with HSV have clinical manifestations that are promoted by states of weakened immunity (1). Discomfort (itch, pain) associated with the eruption of vesicles and emerging erosions, recurrence and aesthetic discomfort significantly reduce their quality of life.

Conventional therapy with nucleotide analogues inhibits viral replication by shortening the duration of symptoms, but does not prevent recurrence. Photodynamic therapy (PDT) is selective, non-invasive, and is not harmful to the patient, and can be used in any clinical condition, in parallel with other therapies, including immunocompromised patients (e.g. transplantation, oncology patients). Recent studies have shown the effectiveness of PDT in the inactivation of different types of virus *in vitro* and *in vivo* (2). The clinical application of PDT in the treatment of recurrent herpes is based mainly on case studies with the use of synthetic dyes as photosensitizers (3–5). The most common photosensitizer used in PDT is 5-aminolevulinic acid (ALA).

The aim of this small pilot study was to evaluate the clinical effectiveness of topical ALA-PDT in the treatment and prevention of recurrences in 8 patients with recurrent herpes simplex (RHS).

MATERIALS AND METHODS

The study was approved by the local ethics committee (KB/6-2014). The patients gave their informed consent prior to enrolment.

Eight patients with RHS were enrolled in the study (2 men, 6 women, age range 25–67 years). Two patients had genital herpes (on the buttock skin) and 6 patients had oral herpes (herpes labialis). Duration of disease ranged from 3 to 6 years, and the number of relapses per year was 4–7. The factors that influenced the appearance of symptoms for the first time, were streptococcal pharyngitis, Hashimoto's disease, chronic severe stress, influenza, and stomach cancer surgery. All patients had received previous treatment with topical acyclovir, 3 patients were also given oral acyclovir (1 patient with genital herpes for 3 months, 2 patients with herpes labialis (1 for 2 months, another for 4 months)) (Table SI[1]). All previous treatments were ended at least 3 months prior to PDT. The patients received no other treatment for HSV during the course of this study.

All patients received one session of ALA-PDT in the early stages of RHS (maculae/papule phase) before the eruption of vesicles. ALA cream (20% with 2% dimethyl sulphoxide; DMSO) was applied to the lesion with a thin border extending to the normal skin (an area of approximately 1.5 cm^2). The lesions were then covered with an occlusive, light-shielding dressing. After 4 h the dressing was removed and the cream was washed off with a 0.9% saline solution.

The lesions were illuminated using red light from a halogen lamp (Penta Lamps, Teclas, Switzerland) at an excitation wavelength of 630 ± 20 nm selected with a bandpass filter with parameters of light: 100 mW/cm^2 and the total dose 120 J/cm^2. Irradiation was performed in a dark room at an intermittent mode (pauses during illumination), without the use of local anaesthetics. The irradiated area was cooled by a fan. After irradiation, the treated sites were covered with a protective dressing. The intensity of burning and pain during the illumination was evaluated using a verbal rating scale (VRS): none, mild, moderate and severe.

Follow-up into the efficacy of ALA-PDT was performed 7 days, then 1, 3, 6 and 12 months after irradiation. The effectiveness of the therapy was assessed according to the clinical response, as: complete response (no recurrence of clinical lesions and prodromic phase), partial response (relapse of prodromic phase only), or no response (recurrence of lesions).

RESULTS

All patients with RHS achieved a good clinical response with ALA-PDT. None of the 8 patients had a relapse of physical evidence of disease during the 12 months of follow-up. However, once during the first 6 months after irradiation 4 patients (1 patient with herpes genitalis and 3 with herpes labialis) experienced prodromal symptoms (partial response): itching and tingling appeared in the place of former lesions, lasting up to several hours and then subsided. Over the next 6 months prodromal symptoms re-appeared once in the same patient with herpes genitalis and in 2 people with herpes labialis. Prodromic signs occurred following occurrence of factors that could provoke recurrent infections: common cold with fever, severe stress, and psycho-physical fatigue (Table SI[1]).

All patients reported pain and burning as the main side-effects associated with irradiation session. Pain as the dominant drawback was reported by 6 patients with herpes labialis: 2 of them rated the pain intensity as moderate, and 4 as severe. Burning sensation as the main adverse effect during irradiation was reported by 2 patients with genital herpes and rated as severe (Table SI[1]). However, no patients discontinued the PDT session due to pain or burning sensation.

Directly after the PDT session swelling and redness was seen at the site of irradiation. The associated inflammation, pain and burning decreased within several hours and was resolved after 24 h in all patients. The use of analgesic and anti-inflammatory drugs was not recommended.

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Approximately 1–2 days after PDT relatively hard crusts were formed and remained longer than usual during the healing period. The process of re-epithelialization took approximately 5–6 weeks. In one patient with herpes labialis, hyperpigmentation of the adjacent healthy skin occurred, and resolved after 3 months. No other adverse effects (such as ulceration, necrosis, scarring or bacterial infections in the irradiated area) were observed.

DISCUSSION

Previous studies have indicated that ALA-PDT has the potential to treat various viral infections (6–9), but there is no study of ALA-based PDT with RHS in humans. The published data is contradictory. An *in vitro* study showed that higher power densities produced a higher rate of viral inactivation than lower fluence rates (10, 11). Others studies demonstrate more viral inactivity at lower, compared with higher, fluence rates for the same total fluence (9, 12). Schindl et al. (13) reported that the total photodynamic damage of light depends on the fluence, irrespective of the fluence rate. However, it is difficult to compare clinical results obtained using different photosensitizers, light sources and doses of light.

Published case reports regarding treatment of recurrent herpes with phototherapy (including laser) using synthetic dyes focus mainly on the effects of reducing the duration of HSV infection symptoms and its accompanying pain, reducing viral titre and acceleration of wound healing, but not on prevention of relapse (3–5, 14). The use of PDT with a relative low dosimetry is indicated in the vesicle phase.

In contrast, in our study, patients were irradiated in the prodromal phase and with a higher dose of light, which caused acute inflammation (pain, erythema and swelling), an extended crusts stage and an extended time of re-epitalization of up to 5–6 weeks. With some preventive measures (pauses during irradiation, cooling fan) the process of illumination was fairly well tolerated and was accepted by patients. Other authors also suggest that more aggressive light parameters yield better viral inactivation and therapeutic effects (15).

The effects of oxidative stress as result of PDT include not only the direct cytotoxic effect, but will also affect the modulation of inflammatory and immune responses. Studies have shown that, in the course of HSV infection, virus particles block suppression of proinflammatory mediators and cause the synthesis of immunosuppressive cytokine-10. Donnarumma et al. (16) demonstrated that laser phototherapy (LPT) in HSV infection acts on the immune response, unblocking the suppression of pro-inflammatory cytokines (tumour necrosis factor (TNF), interleukin (IL)-1b, and IL-6) induced by virions, and limits viral spread from cell to cell.

Pain is a biological signal of inflammation. We hypothesize that the pain during irradiation, induced by a higher dose of light, can advantageously act in the mechanism of antiviral activity of ALA-PDT and contribute to a long remission. Four of our patients experienced prodromic symptoms (partial response to ALA-PDT) and they interestingly found the intensity of side-effects during illumination to be moderate. Therefore: no pain – no effect? Thus, we do not recommend giving anti-inflammatory drugs to the patients after irradiation.

More extensive clinical studies are needed to evaluate the effectiveness and optimize the parameters of ALA-PDT for prolongation of remission intervals in recurrent herpes.

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