

Current Treatments of Muco-Cutaneous Herpes Simplex Virus Infections

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Abstract: Infection by Herpes Simplex Virus (HSV) types I and II represent a worldwide medical problem. After the primary infection the virus establishes a life-long latency in the dorsal root ganglia and recurrences may occur at unpredictable times and rate. The most frequent clinical presentation of HSV infection is recurrent herpes labialis and herpes genitalis. The clinical expression varies according to the body site, the infected cell type, the relationship between HSV and the host immune status. Viral identification techniques such as immunohistochemistry and in situ hybridization on Tzanck smears and muco-cutaneous biopsies are helpful in the diagnosis of atypical cutaneous lesions.

The treatment modalities of HSV infections include the reduction of viral load using antiviral agents, the non-specific immune stimulation of the host and specific vaccination in order to prevent new acquisition and to mitigate symptoms in already infected individuals.

This review addresses various therapeutic options, their mode of action, and clinical value as well as the indications of the various drugs.

INTRODUCTION

The Herpes Simplex Viruses (HSV) types I and II belong to the α -Herpesviridae. They share with the Varicella Zoster Virus (VZV) some similar biological properties including the reproductive cycle, life-long latency in the sensory nerve ganglia, neuro-epidermotropism, and cytopathic effects [1-5]. After the acquisition of primary HSV infection, the virus establishes latency in the corresponding dorsal root ganglia (DRG) [2,6]. Recurrent oro-labial and genital diseases are the most frequently encountered clinical manifestations. The major part of the search for treatments is directed towards these two entities.

This review addresses on the different treatment modalities for muco-cutaneous HSV infections, including their chemistry, mode of action and clinical value. The major indications of the various drugs will be briefly recalled as well as antiviral drug resistance.

TREATMENT MODALITIES

There is currently no curative therapy of HSV infection. In fact, no drugs are available acting on the virus during latency in the DRG. The treatment modalities [7,8] include preventive measures aiming to limit new acquisition and recurrent outbreaks, non-specific immune stimulation, specific anti-HSV vaccination, topical applications of antiseptics, natural sebum components, anesthetics, surfactants, herbal extracts, antivirals, antiinflammatory

drugs, antidepressives, and rhGM-CSF. Chemistry, action mechanisms and therapeutic value are shortly summarized. Only studies conducted in humans are discussed in this review.

PREVENTIVE MEASURES

Preventive measures target the HSV transmission and the triggering factors for recurrent disease. Antiviral prophylaxis can also be attempted.

HSV transmission should be abated in neonates and young infants. A primary herpetic infection may indeed be a serious problem in this pediatric age. During the first year of age, the protective effect of maternal anti-HSV antibodies progressively fades while the immune system is not yet fully developed. Hence, contacts with people exhibiting oro-labial herpes should be avoided. Transmission of HSV from the mother with genital herpes should also be prevented, particularly when the mother acquired primary genital herpes shortly before delivery. In this instance, the mother has not yet mounted an effective antibody response. Hence, the child is not protected by maternal antibodies and is at high risk for developing perinatal herpes. Caesarean section should be proposed and prophylactic antiviral therapy should be offered to the mother [9,10]. Condoms are the most effective way to reduce the risks of transmission of genital herpes, although recurrences on the pubis still represent a possible source of infection [11].

Avoiding triggering factors can efficiently inhibit HSV recurrences. For instance, external photoprotection can show efficacy in sun-triggered HSV eruptions [12]. Prophylactic oral antiviral therapy in order to avoid recurrences of latent HSV infection is now well established in patients with bone marrow and solid organ transplants [13-16], HIV patients

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[17,18], sun-induced HSV recurrences [12, 19-24], burn patients [25-29], and triggered lesions by cosmeto-surgical procedures of the oro-facial region [30-55].

NON-SPECIFIC IMMUNE STIMULATION

Non-specific immune stimulation aims at boosting the patients immune system in order to reduce the recurrence rates and severity of herpetic episodes. Topical agents, non-specific vaccines and systemic immunomodulators have been proposed for such an indication. The mechanisms of action are not clearly elucidated.

Topical Non-Specific Immunostimulation

Dinitrochlorobenzene, Diphenyprone

Topical non-specific immune stimulation uses the high immunogenic potential of dinitrochlorobenzene (DNCB) (C₆-H₃-Cl-N₂-O₄) (Fig. 1) or diphenyprone (DCP) (C₁₅-H₁₀-O) (Fig. 2).

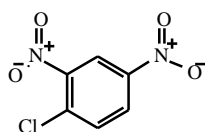


Fig. (1). DNCB.

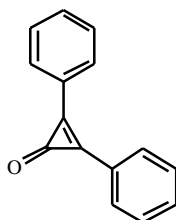


Fig. (2). DCP.

Sensitization is usually induced using an occlusive patch with 2-3% DNCB in vaselin or DCP in acetone applied for 24 hours. Afterwards, different dilutions are tested and the immune stimulation is then performed weekly using the lowest concentration showing erythema in the dilution test. Frequency of applications and percentages of DNCB or DCP have to be adjusted for each patient. No controlled trials studying topical non-specific immunotherapy in herpes labialis and genitalis are available. However, in selected patients, these treatment modalities can achieve promising clinical results at low cost and without significant side-effects.

Imiquimod

Imiquimod (C₁₄-H₁₆-N₄) (1-(2-methylpropyl)-1H-imidazo (4,5-C) quinoline-4- amine (Aldara^o, 3M) is a drug without any direct antiviral activity although exhibiting an

indirect effect by increasing local cytokine production including INF. Other immunological mechanisms are perhaps also operating as well.

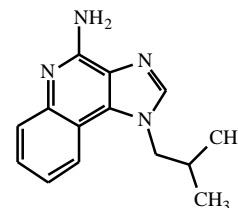


Fig. (3). Imiquimod

This drug currently represents a promising alternative to destructive processes for viral condylomata. Experimental data on the treatment of herpes genitalis in animal models are encouraging [56-59]. However, human data are limited to a study in men with genital herpes [60] and a case report [61]. Sixty men with recurrent herpes genitalis were enrolled to assess the efficacy of imiquimod 1% cream, twice daily during 5 days. This randomized, placebo-controlled, double blind trial demonstrated a statistically significant decrease in the duration of the lesions (5.2 versus 14 days) and more healed patients (23/30 (76.6%) versus 2/30 (6.7%)). Moderate fever, headache, and malaise were noted in 4 patients and 2 other patients reported local irritation [60]. A woman with recurrent genital herpes also benefitted from local applications of imiquimod cream three times a week after the interruption of suppressive oral aciclovir therapy [61].

As imiquimod is an inducer of local INF production, no significant effects are to be expected in the sensory ganglia. In fact, it is still unknown whether a clinically effective memory response remains after treatment interruption, as observed in animal models [56-59]. However, as documented in the preliminary trial, imiquimod limited the disease duration and severity, but did not affect the disease relapse rate. The precise place of imiquimod in the therapy of recurrent genital herpes remains to be determined by larger placebo-controlled, double blind, randomized trials. Furthermore, irritation by the drug remains a frequently observed problem, particularly in men.

Interferon Alpha

Interferon (IFN -2a) (Roferon-A, Roche) has no direct antiviral capacities, but acts as an indirect antiviral agent through immunological mechanisms. The efficacy of IFN -2 a has been studied in a prospective open trial with 97 patients suffering from at least 5 yearly recurrences of genital herpes [62]. After subcutaneous injections of IFN -2 a (3x10⁶ units, three times a week for 4 weeks, repeated at month 3 and 6) 51 patients remained recurrence free for 2 years. The mean healing time was decreased from 8.5 to 2.5 days after IFN -2a treatment and the number of recurrences per year was reduced from 7.5 to 2.6 after therapy. The most significant side-effect was a flu-like syndrome after the injections. The place in the treatment of herpes simplex infections by IFN -2a remains to be clarified and currently no data is available comparing the efficacy of IFN -2a versus specific antiviral drugs.

The effect of local applications of hINF -2 (2×10^6 IU/g) incorporated in a hydrophilic cream and in a gel was assessed in a double-blind, placebo-controlled, comparative study conducted in 60 men with first episodes of genital herpes. The study demonstrated that patients treated with leukocyte hINF- 2 cream had both significantly shorter mean duration of lesions than gel and placebo recipients (5.3 days versus 8 days and 13 days respectively). Feverish feelings, moderate headache, malaise and myalgia were reported in 18% of the patients. In a follow up study for 24 months 4 patients relapsed out of 31/60 cured patients after 18 months [63]. Another double-blind, placebo-controlled study confirmed the clinical efficacy of hINF -2 cream three times a day daily for 5 days (2×10^6 IU/g) in 60 patients with first episode genital herpes. hINF -2 treated patients had significantly shorter mean healing time than placebo recipients [64].

Systemic Non-Specific Immune Stimulation Using Vaccines

BCG, smallpox, polio, influenza and yellow fever vaccinations have been advocated as non-specific immune boosting therapies for recurrent HSV infections. After BCG vaccination for recurrent herpes, all patients remained herpes free for 4-6 months. Longer follow-up demonstrated 19% and 9% of herpes-free patients of after 3 and 10 years, respectively [65]. A double-blind, prospective randomized trial on 24 patients neither confirmed the protective effect of yellow fever vaccination on recurrent herpes labialis [66]. However, it is generally accepted that these therapies are not active and no longer recommended in HSV disease.

Systemic Non-Specific Immune Stimulation Using Drugs

The non-specific immunomodulators, such as oral levamisole ($C_{11}-H_{12}-N_2-S$) (Fig. 4) and isoprinosine ($C_{10}-H_{12}-N_4-O_5 \cdot 3C_9-H_9-N-O_3 \cdot 3C_5-H_{13}-N-O$) (inosine pranobex, 50-70

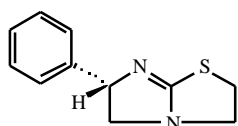


Fig. (4). Levamisole

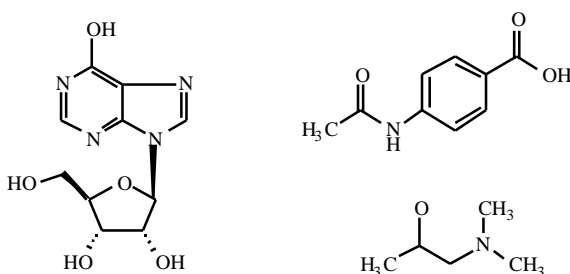


Fig. (5). Inosine pranobex

mg/kg in 4 daily intakes, Synthelabo^o) was rather disappointing in the treatment of recurrent muco-cutaneous HSV infections.

Indeed, the superiority of antivirals was demonstrated in comparative trials in the treatment of first-episode [67] and recurring genital herpes [68]. Accordingly, these treatment options are not routinely recommended.

Specific Vaccines

The main goals of vaccination are protection against primo-infection, reduction in the severity and rate of recurrences, and lowering HSV transmission risk between individuals. Several approaches are used such as vaccination with chemically or heat-shock inactivated virus, purified viral glycoproteins, recombinant viral proteins, viral glycoprotein subunits, as well as live-attenuated, DNA, and DISC (disabled infectious single cycle) HSV [69-72]. There is a discrepancy between vaccination results in animals that usually provide excellent results compared with the poor results in most human trials. In fact, the interplay between the virus and the host immunity is more complex in humans than in animal models [70]. Furthermore, the protective effect of most vaccines is merely priming an immune response, rather than inducing a complete sterilizing immunity. Hence, the vaccines prevent the disease but not the initial HSV replication. During HSV primoinfection there is, however, no viremia but a local infection with subsequent establishment of latency in the sensory DRG [73]. The local infection and latency may thus explain why circulating antibodies do not interrupt the initial events of mucosal HSV infection. Effective protection against new HSV infection needs more than the presence of neutralizing serum antibodies. These facts also explain the efficacy of VZV vaccination in the prevention of varicella contrasting to the fairly poor outcomes of HSV vaccine trials.

Vaccination efforts have mainly been directed towards herpes genitalis due to its impact on public health. Only a few human trials are published on recurrent herpes labialis and ocular herpes.

One of the first randomized multicentric, placebo-controlled vaccination trials used the Skinner vaccine (intracellular subunit HSV type I vaccine NFU.Ac.HSV-1(S-) MRC) in patients with recurrent genital herpes. The vaccine was administered at 0, 1 and 2 months and produced a decrease in the severity but not in the frequency of the outbreaks [74]. Another trial using a killed HSV vaccine demonstrated a decrease duration of the active disease (11.59 versus 65.11 days) in 142 patients with recurrent genital and labial herpes [75]. The efficacy of heat-shock inactivated HSV I vaccination was evaluated in a small series of patients with recurrent HSV I keratitis/kerato-uveitis. After a one-year follow-up the number and duration of the recurrences was reduced [76].

A large randomized, double blind and placebo-controlled trial evaluating the protective effect of a vaccine containing two major HSV II surface glycoproteins gB2 and gD2, administered at 0, 1 and 6 months with a follow-up of one

year, was conducted in 2393 HSV II seronegative individuals [77]. The endpoint of the study was defined as HSV II seroconversion. The new acquisition in the two groups was 4.6 and 4.2 % of the patients respectively. The follow-up demonstrated no effects on the duration of the primary infection and on the number of recurrences. Vaccination achieved high levels of anti-HSV II specific antibodies. No curative and preventive effects were obtained with this type of vaccine.

Another study evaluated the efficacy of a vaccine containing recombinant gD2 protein in the reduction of the number of relapses of genital herpes [78]. This double blind, placebo-controlled study included 98 patients and demonstrated a reduction of clinical (0.42 versus 0.55) and virological (0.18 versus 0.28) monthly recurrences, as well as a decrease in the frequency of relapses in the year following the vaccination (4 versus 6).

A vaccine with the recombinant HSV II glycoproteins gB and gD was administered at 0, 2, 12 and 14 months in patients with genital herpes. In this placebo-controlled trial with a follow-up of 18 months the monthly rate of recurrences was not significantly decreased, although there was a positive effect on the reduction of the severity and duration of the relapses in the vaccinated group [79].

In brief, much work still needs to be done in vaccination approach of herpes infection. From a clinical point of view, the currently results with vaccines cannot match with those obtained using antiviral treatment.

ANTISEPTICS

The use of topical antiseptics has been studied for the treatment of recurrent oro-labial and genital herpes. Topical glutaraldehyde 2% ($C_5-H_8-O_2$) (Fig. 6) [80,81] and butylated hydroxytoluene (benzyl alcohol C_7-H_8-O) (Fig. 7) [82] have been advocated in the treatment of recurrent herpes labialis.

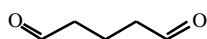


Fig. (6). Glutaraldehyde

The risk of inducing allergic contact dermatitis cannot be dismissed. In a pilot study, external and intravaginal preparations of povidone-iodine ($(C_6-H_9-N-O)_x \cdot x \cdot I_2$) (Betadine^o) (Fig. 7) exhibited a positive reduction on the disease duration in 10 patients with genital HSV infection [83].

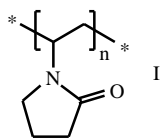


Fig. (7). Povidone iodine

An open-label, randomised trial including 72 patients with cold sore demonstrated the efficacy of povidone-iodine 10% applied twice daily in decreasing the period during which infectious HSV could be recovered at culture [84]. Topical applications of ether ($C_4-H_{10}-O$)(4x/day for 7 days) were found to be ineffective for the treatment of genital HSV infection [85].

In summary, some antiseptics show anti HSV activity enhancing the resolution of recurrent HSV-associated symptoms. No clear cut comparative data are available with topical antivirals.

NATURAL SEBUM COMPONENTS

Undecylenic acid ($C_{11}-H_{20}-O_2$) (Fig. 8) is a mono-unsaturated fatty acid present in human sebum. It exhibits antibacterial, antifungal and antiviral properties. Undecylenic acid 15% cream 5-6x/day until healing reduces viral shedding in recurrent herpes labialis, but clinical benefits appear minimal and largely restricted to patients starting the treatment during the prodromal phase [86].

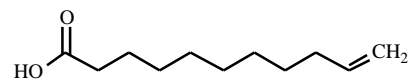


Fig. (8). Undecylenic acid

ANESTHETICS

Topical applications of anesthetics aim to relief pain experienced during recurrent herpes. A double blind, placebo-controlled trial evaluated 1.8% tetracaine ($C_{15}-H_{24}-N_2-O_2$) (Fig. 9) cream 6x/d up to 12 days in recurrent herpes labialis.

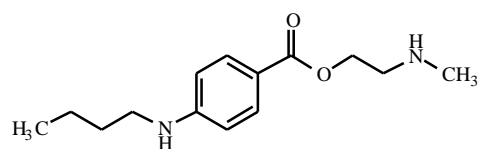


Fig. (9). Tetracaine.

When applied frequently it was found to be successful in reducing the healing time and itching, although pain scores were unchanged compared to placebo [87].

SURFACTANTS

Surfactants can inactivate HSV *in vitro* by damaging the envelope. However, no clinical effect on genital herpes was observed in a clinical trial using the non-ionic surfactant nonoxynol-9 ($C_{33}-H_{60}-O_{10}$) (Fig. 10) [82].

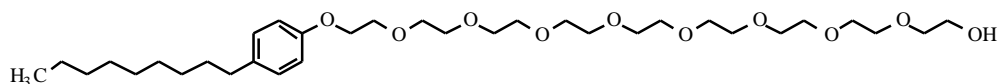


Fig. (10). Nonoxynol-9.

Biosurfactants such as surfactine, are promising agents that merit controlled studies.

HERBAL EXTRACTS

No precise action mechanisms are described for purported herbal therapies. A double-blind, placebo-controlled, randomized trial was carried out including 66 patients with recurrent herpes labialis using a balm mint extract cream applied 4 times daily for 5 days. This therapy appeared to shorten the eruption duration and associated symptoms. Some indication exists that the intervals between herpes lesions might be prolonged [88].

ANTIVIRALS

Antiviral therapy aims to inhibit the viral replication in order to diminish the viral load and hence the severity of the infection. Antiviral agents can be administered topically, orally or intravenously.

Topical Antiviral Agents

A large variety of topical antiviral drugs is available for the treatment of oro-labial and genital herpes. Such treatments include tromantadine 1% ointment 6x/day for 5-14 days [89,90], aciclovir (ACV) 5% cream 5x/day for 5 days [91-94], adenine arabinoside (Ara-A) 3% ointment, 10% cream 6x/day for 7 days [95,96], edoxudine (EDU) 3% cream 6x/day for 5 days [97], idoxuridine (IDU) 15% in DMSO 80% 3-6x/day for 3-4 days [98], trifluorothymidine (TFT) 5% ophthalmic solution [99-101], SP-303 15% ointment [102] foscarnet (PFA) 1% cream [103-108], cidofuvir (HPMPC) 1, 3, or 5% cream or gel 1x/day for 4 days [109-113], and penciclovir (PCV) 1 and 5% cream every two hours for 4 days [114-116].

The clinical efficacy of these various antiviral agents has recently been reviewed [117]. Currently, the most frequently used topical drugs are ACV, PCV, HPMPC, and Foscarnet.

ACV ($C_8-H_{11}-N_5-O_3$) (2-Amino-1,9-dihydro-9-((2-hydroxyethoxy)methyl)-6H-purin-6-one) (Fig. 11) remains the gold standard therapy of HSV infection since more than 15 years [118].

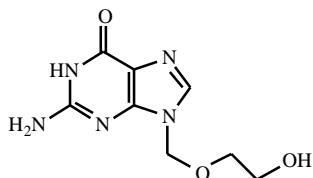


Fig. (11). Aciclovir.

This nucleoside analogue is phosphorylated by the viral thymidine kinase (TK) into ACV monophosphate. Subsequently, two further phosphorylations are required by cellular TKs to produce the triphosphate (TP) form of ACV that is the active form of the drug. ACV TP is an obligate chain terminator and hence inhibits viral DNA polymerase and consequently viral replication [118]. The efficacy of ACV has been studied with a 5% cream and 5 and 10% ointments. Topical ACV showed a reduction in the duration of viral shedding and lesions of recurrent herpes labialis in some studies [119,120]. In contrast, it was found not to be statistically significantly effective in other trials [93,94,121,122]. In primary and recurrent genital herpes, ACV 5% ointment reduced the duration of viral shedding, pain relief and time to loss of crusts [92, 123] In contrast, another trial including 309 patient showed no significant effect of topical ACV the clinical signs of recurrent genital herpes [124].

PCV ($C_{10}-H_{15}-N_5-O_3$) (Fig. 12) is a synthetic acyclic guanine derivative displaying antiviral activity against HSV and VZV. PCV is also a TK-dependant antiviral compound that has to be phosphorylated three times into an active TP derivative. PCV TP is a potent inhibitor of viral DNA polymerase although the affinity for the polymerases is lower than that of ACV [125,126]. PCV is not an obligate chain terminator. It has a prolonged intracellular half-life compared to ACV. Both early and late initiation of PCV 1% cream applied every 2 hours for 4 days on recurrent herpes labialis reduce healing time, viral shedding, and pain [114]. Another large randomized, double-blind placebo-controlled trial, evaluating the efficacy of PCV 1% cream (every 2 hours for 4 days) in UV-induced relapsing herpes labialis demonstrated significantly improved clinical scores including decreased healing time and eruption associated symptoms [116].

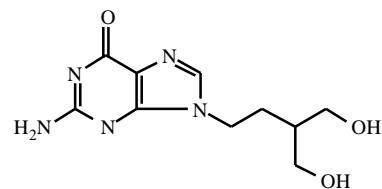


Fig. (12). Penciclovir

HPMPC ($C_8-H_{14}-N_3-O_6-P$) (S)-1-(3-hydroxy-2-phosphorylmethoxypropyl) cytosine (Cidofovir) Vistide[®] (Fig. 13), an acyclic nucleoside phosphonate derivative exhibiting a broad antiviral spectrum, has a long-lasting intracellular antiviral action.

Cidofuvir gel (1, 3 and 5 % once daily) has been studied in a double-blind, placebo-controlled, randomized trial including 96 patients for the treatment of recurrent genital

herpes and showed a significant decrease in viral shedding time and a trend towards reduced healing time. Toxic local reactions were dose-dependent and observed in 5, 19 and 22% of the patients according to the 3 concentrations, respectively [109]. As HPMPC is not dependent on viral TK activation, it represents a therapeutic alternative against TK-negative HSV strains [110,113]. HPMPC gel (0.3 and 1%, 1x/day for 5 days) was studied in a randomized double-blind trial for ACV resistant HSV infections in AIDS patients and demonstrated significant improvements in healing time, pain reduction and viral shedding [112]. Topical HPMPC is also a therapeutic alternative in ACV and PFA combined resistant HSV infection [111].

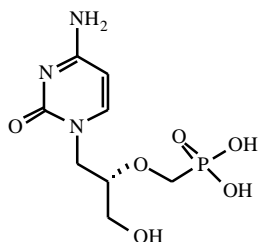


Fig. (13). HPMPC

PFA (C-H₃-O₅-P) (Fig. 14) is an inhibitor of viral DNA polymerase and functions as a chain terminator. Hence, the drug is not dependent on viral TK to be activated.

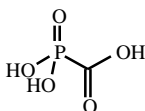


Fig. (14). PFA.

Early applications of 0.3% foscarnet cream every 2 hours for recurrent genital herpes has shown a quicker resolution time of lesions in men only [127,128]. However, 3% foscarnet cream applied every 2 hours was not effective in recurrent herpes labialis [129] although the same formulation with 8 applications daily for 7 days showed a trend towards quicker healing time and pain reduction in UV-induced lesions [106]. The major indication of topical and intravenous PFA remains the potential activity in TK-negative HSV strains, particularly encountered in HIV-infected patients and other immunocompromised individuals. Several case reports illustrate the place of PFA in the armamentarium against infections exhibiting TK-dependent drug resistance. In 11/15 patients 1% foscarnet cream produced a complete resolution of symptoms in a phase I/II, open-label, nonrandomized multicenter trial for HSV lesions that were clinically unresponsive to systemic ACV treatment including 20 AIDS patients [103]. Furthermore, its efficacy was shown in ACV-resistant HSV I muco-cutaneous infections in an immunocompromised patient [107] and in chronic ACV-resistant genital herpes [108]. Isolated PFA failure [105] or combined PFA and ACV failure [130] have, however, also been reported.

There is evidence that the penetration of topical antiviral drugs is poor and thus requires frequent applications. However, skin penetration enhancers such as ethosome, a liposome carrier, improved delivery of topical 5% ACV versus commercial 5% ACV cream and a drug-free vehicle suggested an improved clinical efficacy in a 2-armed, double-blind, randomized clinical trial on 61 herpetic episodes in 40 subjects [131]. Again, the additional use of the surfactant nonxynol suggested an enhanced penetration and efficacy of topical interferon [132].

In summary, all the topical antiviral agents demonstrate a shortened disease course and an alleviation of the associated symptoms when the drug is administered soon after the disease onset, and when applied frequently.

Systemic Antiviral Agents

Aciclovir

Oral and intravenous ACV formulations have been extensively studied in HSV pathology. ACV suspension 15 mg/kg five times a day for seven days, or placebo was administered in 72 children with herpetic gingivo-stomatitis lasting less than 72 hours. This randomized double blind placebo-controlled study showed that children receiving ACV had oral lesions for a shorter period, significantly shorter time with viral shedding, earlier disappearance of fever, extraoral lesions, and swallowing difficulties than the placebo group. Further studies are, however, warranted to establish the ideal dosing regimen [133]. In contrast to topical prophylactic ACV, continuous prophylactic oral ACV (400-1000 mg/day) was effective in frequently recurring herpes labialis, reducing the relapse rate by 50-78% [19,134]. Oral ACV is also active against severe oro-labial recurrences when rapidly initiated. Long-term continuous oral ACV in the prophylaxy of recurrent herpes labialis is also effective [19], but is costly [135]. Short-term preventive oral ACV therapy was effective in preventing sun-induced recurrent herpes labialis [21].

The efficacy of ACV in reducing symptoms, improving healing rates, and pain relief has been shown in first-episode genital herpes using oral [136,137] and intravenous administrations [138-141]. Patient-initiated ACV treatment has been shown to be effective in recurrent genital herpes [142-144]. Suppressive, prophylactic treatment of genital herpes is also possible using long-term administrations of oral ACV (400-1000 mg/day). The frequency and severity of recurrent genital herpes was significantly reduced in the majority of the patients and about 70 % of them remained completely recurrence free during therapy [145-148]. Drug resistance has never been clinically relevant in immunocompetent patients with recurrent genital herpes. The crucial question addressing ACV reduction in asymptomatic viral shedding, thus decreasing the risk of viral transmission, was addressed in a double-blind, placebo-controlled, crossover clinical trial (ACV 400 mg twice daily for 70 days, followed by a 14-day washout period, and then placebo for 70 days). Asymptomatic viral shedding in 34 women showed a reduced frequency, as evidenced by daily viral cultures. Hence, ACV can help in the prevention of HSV-2

transmission [149]. Oral ACV showed efficacy in the following indications : herpetic whitlow (2 g/day in three doses for 10 days) [150], traumatic induction of herpes recurrences [151-153], moderate eczema herpeticum (200 mg 5x/day for 5 days)[154], prophylaxis for dermo-cosmetic procedures of the oro-facial region (200 mg 2-5x/day 2 days before intervention), prevention of sun-induced HSV recurrence (200 mg 5x/day)[19], and prophyl-axis for HSV-associated erythema multiforme (HAEM) (400mg 2x/day)[155-161].

Intravenous ACV has also proven its efficacy in the treatment of HSV infection in the immunocompromised patients [162-168], the neonatal infection (10-20 mg/kg/8 hours for at least 21 days)[169], and severe eczema herpeticum (10 mg/kg/ 8 hours for 5-7 days).

Penciclovir, Famciclovir

The efficacy and safety of intravenous PCV (5mg/kg/8 hours and 5mg/kg/12 hours) versus ACV (5mg/kg/8 hours) for the treatment of HSV infections in 342 immunocompromised patients were studied in a double-blind, controlled, and multicentric study. Equivalence with ACV was demonstrated for both q12h and q8h PCV regimens. No statistically significant differences were yielded in the rates of complete healing and cessation of viral shedding between the three groups. In addition, there was no statistically significant difference between PCV q12h or q8h, compared with ACV q8h, for the resolution of pain. Hence, PCV q12h may be considered as valuable intravenous therapy for muco-cutaneous HSV infection in immunocompromised patients. It offers a reduced frequency of dosing compared with ACV q8h [170].

To overcome the poor oral PCV bioavailability, FCV ($C_{14}-H_{19}-N_5-O_4$) (Fig. 15) was developed as an oral prodrug of PCV, reaching a 77% oral bioavailability. It is the diacetyl ester of 6-deoxy PCV.

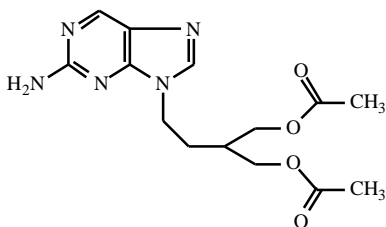


Fig. (15). Famciclovir.

It is rapidly absorbed after oral administration and converted into PCV by oxidative metabolism [126]. Clinical studies of oral FCV have addressed the therapy of recurrent herpes labialis in immunocompetent [171] and immunocompromised subjects [172].

Although no specific trial is available, FCV (250 mg, 3x/day for at least 5 days) is an effective therapy for primary oro-labial herpetic gingivostomatitis. The efficacy of oral FCV (125, 250, or 500 mg or placebo 3x/day) was evaluated in patients with experimental ultraviolet-induced herpes

labialis. The treatment was initiated 48 h after UV exposure. The maximal lesion size and median time to healing were reduced in a dose-proportional manner. Evaluations of higher drug doses for herpes labialis would be welcome [171].

In a randomized, placebo-controlled trial of patient-initiated oral FCV (125, 250, 500 mg/day for 5 days), as episodic therapy of genital herpes, all dosages were significantly more effective than placebo in the reduction of healing time, viral shedding, and pain assessments [172].

FCV has also been studied in the long-term prophylaxis of recurrent genital herpes. A study including 375 women presenting at least 6 annual recurrences compared FCV (125 mg 1x/day, 125 mg 2x/day, 250 mg 1x/day, 250 mg 2x/day, 500 mg 1x/day and 500 mg 2x/day) versus placebo during 4 months. The active treatments induced a significant increase in time until the first relapse compared to placebo (114 versus 82 days in the 125 mg 1x/day group, 120 versus 82 days in the other group) [174]. Another trial including 455 patients with at least 6 annual relapses studied the efficacy of oral FCV for 1 year (125 mg or 250 mg 3x/day, 250 mg 2x/day and placebo) [175]. All the dosages prolonged significantly the disease-free duration.

FCV therapy for recurrent herpes labialis and genitalis in the immunocompromised subject has also been addressed. In 48 HIV-infected patients, a double-blind, placebo-controlled, crossover trial evaluated the effect of FCV (500 mg orally twice daily, or placebo for 8 weeks) on the frequency of oro-labial and genital HSV reactivation. HSV was isolated on 122 of 1114 (11%) placebo days compared with 9 of 1071 (1%) FCV days. Hence, oral FCV results in significant reductions in the HSV-associated symptoms as well as in the symptomatic and asymptomatic shedding of HSV among HIV-positive persons [172].

Another reported indication of oral FCV is the prevention of HSV recurrences in patients undergoing laser resurfacing (FCV 2x125mg/d in patients without a history of RHL and 2x250mg/day in those with a history of RHL) [33].

Valaciclovir

Valaciclovir ($C_{13}-H_{20}-N_6-O_4.Cl-H$) (VCV) (Fig. 16) is an L-valyl ester of ACV and was designed to overcome the poor oral ACV bioavailability.

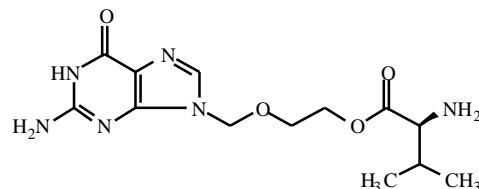


Fig. (16). Valaciclovir.

After oral intake VCV is converted into ACV with a bioavailability of 63% [176-179]. VCV has mainly been studied in first-episode and recurrent genital herpes and as

suppressive therapy for recurrent genital herpes. An international, multicenter, randomized, double-blind clinical trial compared VCV (1000 mg 2x/day for 10 days) and oral ACV (200 mg 5x/day for 10 days) in 643 adults with first-episode genital herpes. VCV and ACV did not differ significantly in efficacy with respect to duration of viral shedding, time to healing, duration of pain, and time to become asymptomatic. VCV proved to be as effective and well tolerated as oral ACV in the treatment of first-episode genital herpes. Furthermore, it offers the advantage of a more convenient dosing regimen [180].

Patient-initiated VCV (500 mg 2x/day for 5 days) as episodic therapy was compared to ACV (200 mg 5x/day for 5 days) in a randomized, double blind trial including 739 patients with recurrent genital herpes [181]. Similar efficacy was shown in both groups regarding reduction of lesion duration and pain. VCV presents the advantage over ACV of two daily intakes. These data were confirmed in another double blind placebo-controlled study including 987 patients with genital herpes where VCV 500 mg/day for 5 days was equally effective as VCV 1000 mg/day in the reduction of duration and eruption-associated symptoms (Sprauce 1996). A third trial proved the equal efficacy of self-initiated VCV 1000mg once daily versus VCV 500mg twice daily in patients with recurrent herpes genitalis [182].

Long-term suppressive prophylaxy for frequently recurring genital herpes with oral VCV has also been evaluated [183,184]. In a 16-week study, VCV (500 mg/day) was compared to placebo in 382 patients with more than 8 annual recurrences [183]. The VCV group showed a significant increase in time until the first relapse compared to placebo. Another one year placebo-controlled study including 1479 immunocompetent subjects comparing different dosages of VCV (250, 500, or 1000 mg/day or 250 mg 2x/ day) demonstrated that all groups were significantly more effective than placebo in the prevention of recurrences [184]. Subgroup analysis showed that VCV 500 mg/day was the optimal dose for patients with less than 10 recurrences per year and that 1000 mg/day was the best choice for patients suffering from more than 10 recurrences per year. In both studies, the tolerance and security profiles were excellent. An open-label, multicentric clinical study was conducted in 127 patients to evaluate the number of genital herpes recurrences during 1 year of suppressive VCV therapy (500 mg once daily) [185]. The results showed that 65% of the women and 69% of the men remained recurrence free during the trial.

It is impossible to directly compare the results of the FCV and VCV studies as the VCV studies included patients with more severe genital herpes and more frequent outbreaks.

HPMPC

Once weekly intravenous administration of HPMPC was successfully used in the treatment of an ACV- and PFA-resistant HSV I lesion in an immunocompromised patient [186]. Disadvantages are the complexity of administration and the side- effect profile including nephrotoxicity and neutropenia occurring in 15% of the patients. Probenecid and

NaCl 0.9% perfusions may be used to reduce the incidence and severity of nephrotoxicity in patients receiving cidofovir. The topical gel formulation is as effective and lacks the systemic adverse effects [113].

Foscarnet

Intravenous administration of PFA (40-60mg/kg/8hours for 7-10 days) may be attempted in muco-cutaneous HSV infections exhibiting ACV resistance in immunocompromised patients [187,188]. Nephrotoxicity is the major side-effect of intravenous PFA therapy and dosages should be reduced in case of renal insufficiency. PFA therapy may, however, fail in some ACV-resistant HSV infections [105,130].

Anti-Inflammatory Drugs

To explore the effect of acetylsalicylic acid (C₉-H₈-O₄), 21 volunteers with recurrent HSV infection (19 herpes labialis, 2 herpes genitalis) received 125 mg of aspirin daily at the first symptomatic HSV recurrence. The aspirin-treated patients had significantly fewer days of active HSV infections and milder symptoms than did the controls. Aspirin may be beneficial in patients with recurrent HSV infections but warrants further placebo-controlled studies [189].

Antidepressives

Lithium carbonate (C-H₂-O₃,2Li) exhibits antiviral activity by inhibiting viral DNA synthesis [190]. Small clinical studies presented rather disparate results, ranging from a complete suppression of recurrent herpes labialis in one patient [191], to a mild decrease in the frequency and intensity of genital herpes recurrences [192,193], and a significant improvement in the rate of herpes labialis recurrences [194]. Due to its antidepressive effects, the place of lithium in the treatment of recurrent herpes infections remains clearly very limited.

Recombinant human Granulocyte Macrophage-Colony Stimulating Factor

Subcutaneous injection of 300 mg/day of rhGM-CSF for 6 days was used in a woman with HSV recurrent genital infection non responsive to antiviral treatment. Her polymorphonuclear cell and monocyte functional capacities were depressed. After treatment, normalization of the immune functions was observed with a progressive clearing of clinical manifestations [195]. This treatment option has no direct antiviral properties but restores some altered immune functions involved in the control of viral infections.

Management of Resistance

HSV resistance to usual antiviral therapy in the immunocompetent population steadily remains at about 3%. It is not a clinical concern even during long-term suppressive treatment regimens for herpes genitalis. During suppressive therapy the virus probably remains in a latent state. An eventual viral reactivation is rapidly halted by the antiviral prophylaxis, hence preventing long term exposure of an actively replicating virus to an antiviral permitting the development of eventual resistance. However, the reverse is

encountered in the immunosuppressed patient, particularly in the HIV-infected patients who are frequently under long-term suppressive antiviral therapy, in whom ACV-resistant HSV strains are an emerging clinical problem [99,196-198]. In this patient group, the presence of actively replicating virus is probably much more frequent, increasing the exposure time to the antiviral and hence, increasing the possibility of resistance development. The disease course of ACV-resistant HSV strains is often chronic and progressive with prolonged viral shedding. ACV-resistance is caused by mutations either in the thymidine kinase or the DNA polymerase genes, resulting in decreased or absent HSV thymidine kinase production, altered affinity of the thymidine kinase or DNA polymerase for ACV TP [199]. TK deficiency accounts for approximately 95% of the clinical isolates

When resistance is clinically suspected, a culture should be obtained for drug-susceptibility testing [9]. Drug-susceptibility testing in HSV infections is a helpful tool in decision making for treatment strategies in contrast to VZV infections where drug susceptibility testing on cultures is too slow to be of significant clinical relevance [200].

It is generally suggested to change the antiviral therapy after 7-10 days when drug resistance is clinically suspected [99]. The first alternative is PFA (40-60mg/kg/8hours) [187,188] to be initiated for at least 10 days or prolonged until the clinical clearing of the lesions. A controlled trial demonstrated that PFA provided superior efficacy and less frequent serious side-effects than intravenous vidarabine (15mg/kg/day) [196]. When PFA fails [105,130], several other alternative antiviral drugs can be offered. Topical ophthalmic trifluridine (1% solution) was studied in an open label pilot trial for the treatment of chronic mucocutaneous HSV infections unresponsive to ACV therapy in 24 AIDS patients. Seven patients presented complete healing of lesions and 7 other patients noted partial reduction in lesion area. Eight patients continued to develop new lesions outside of the treatment area while on study, reflecting the restricted local effect of this therapy [100]. Topical trifluridine may be a useful alternative in selected patients [100,101]. Topical HPMPC gel is another option [113]. A small randomized, double-blind, multicenter trial evaluated the effect of topical HPMPC 0.3% or 1% gel vs placebo, ointment for 5 days on ACV-unresponsive HSV infections in AIDS patients. Ten of the 20 HPMPC-treated patients presented partial or complete clearing of lesions [112]. Once weekly intravenous HPMPC was used in an ACV- and PFA-resistant HSV I lesion [186]. Whatever the antiviral drug used, the relapse rates of HSV infections are especially high in this patient category.

CONCLUSION

Infections by HSV types I and II represent a frequently encountered medical problem involving both the immunocompetent and immunosuppressed patient.

Current therapeutic modalities include preventive measures, non-specific immune stimulation, specific anti-HSV vaccination, topical applications of antiseptics, natural sebum components, anesthetics, surfactants, herbal extracts,

antiviral agents, antiinflammatory drugs, antidepressives, and rhGM-CSF. The most effective prophylactic and therapeutic option against HSV infection remains the oral or intravenous administration of antivirals. Aciclovir, a thymidine-kinase dependant anti-HSV agent, is the gold standard therapy since more than 15 years. Today, aciclovir tends to be replaced by newer antiviral agents such as valaciclovir and famciclovir, the oral prodrugs of aciclovir and of penciclovir, respectively. The non-thymidine kinase dependant antiviral drugs HPMPC and foscarnet are helpful therapeutic alternatives in case of aciclovir-resistant HSV strains in the immunocompromised host

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