Review

Herpes simplex virus keratitis: an update of the pathogenesis and current treatment with oral and topical antiviral agents

Short running title: Herpes simplex virus keratitis and antiviral agents

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ABSTRACT

Ophthalmic herpes simplex viral keratitis (HSVK) is responsible for a range of ocular manifestations from superficial epithelial disease to stromal keratitis and endotheliitis. The Herpetic Eye Disease Study (HEDS) has guided the management of herpetic eye disease for almost twenty years, but newer medications such as valacyclovir are now available and are considered to have better bioavailability than acyclovir. In this review, we examine the existing evidence on the pathogenesis of different HSVK disease modalities and the role of oral and topically administered antiviral drugs in the treatment of herpes simplex viral keratitis.

Keywords: Valacyclovir, Acyclovir, Ganciclovir, Herpes Simplex Keratitis

INTRODUCTION

Ocular herpes simplex infection and disease manifestation are a major cause of visual morbidity worldwide. It is estimated that 90% of adults are seropositive for the herpes simplex virus (HSV) antigen and approximately 500,000 cases of active ocular herpes simplex infection are seen per annum in the United States[1]. The prevalence of antibodies against the HSV in serum and tears increases with age and is related with reduced corneal sensation, neurotrophic keratitis and stromal opacities.[2] Interestingly, only 20-30% of herpes inoculated individuals develop clinical manifestations, with the majority of patients suffering from herpes labialis[3]. Ocular infection is usually unilateral but bilateral cases occur at a rate of 1.3-12% and are usually seen in younger patients[4].

Herpes simplex infection can involve both anterior and posterior segments of the eye but most commonly it is seen as a corneal epithelial infection, namely a dendritic ulcer. HSV can affect any and all layers of the cornea but it is the relapsing and recurring stromal and endothelial disease that renders the greatest morbidity through corneal scarring and neovascularisation. Disciform keratitis accounts for

approximately 2% of initial ocular HSV presentations but is responsible for 20-48% of disease recurrences[1,3,5].

Different treatment modalities against HSV have been developed to date and are also the field of current research in an effort to achieve better disease control and counteract resistance of the virus to currently used medication. Topical and systemic treatments exist, each one with specific mode of action and sometimes combination regimens are used to enhance the therapeutic outcomes.

THE STRUCTURE OF HSV

Herpes simplex virus exists in two forms: HSV-1 and HSV-2. HSV-1 is the more common sub-type manifesting in ocular infections[6]. HSV-1 has a linear double stranded DNA, comprising of 152 kb and approximately 80 genes[7]. The HSV-1 virion is approximately 120-300nm in size, consisting of an electroopaque core which contains the genome, a caspid or shell, a tegument and an envelope (Figure 1). Adherent to the capsid is the tegument, a layer that contains proteins essential for virus survival in host cells e.g. virion host shut-off protein (VHSP). HSV-1 has an outer lipid bi-layer, or envelope, with embedded glycoproteins (gB, gC, gD, gH) that facilitate virus to host cell attachment, fusion and permeability[8].

Viral DNA transcription, replication and viral capsid assembly occur in the host nucleus with DNA polymerase essential for HSV-1 replication[9]. Synthesis of the tegument proteins occur in the cytoplasm[9], with HSV viral replication taking between 18 and 20 hours[8,9]. HSV infection can occur through direct cell to cell inoculation but HSV-1 can also be transported along sensory neurons and establish infection distant to its initial infection site. By assuming latency in sensory neurons or ganglia, HSV can re-emerge in an active form at a later date[8].

LATENCY

HSV replication, usually leads to host cell death. However, in neuronal cells, viral replication is limited and is less destructive to its host cell, allowing the virus to remain dormant, reactivating at a later stage. This is known as latency. The HSV-1 genome exists in three states: linear, circular and concatemeric[10,11]. A linear state is the preferred template for DNA transcription during replication. However, during viral latency, the HSV-1 genome is found in a circular form. Studies with mice have permitted the identification of viral transcripts called Latency-Associated-Transcripts (LATs) thought to be the key in inducing and maintaining viral latency. The LAT region has not been shown to encode for any proteins but is thought to be involved in neuronal survival, suppression of apoptosis, induction of latency and reactivation from latency[12]. During viral reactivation, expression of LATs decreases although the exact mechanism by which LATs function remains under investigation.

Ocular infection with HSV can occur directly through direct droplet spread or as a secondary infection, where an individual who has experienced previous exposure to HSV in non-ophthalmic parts of the trigeminal dermatome will subsequently manifest ocular HSV[13].

HSV has been found in the brainstem and trigeminal ganglia (TG) and the latter is thought to be the principle site for HSV-1 latency. Virus is transported to the eye in a retrograde fashion along sensory axons although studies have also confirmed the presence of HSV in its latent form in the cornea but this still remains controversial[5,14].

The risk of HSV disease after primary infection is approximately 10% within the first year[5]. The trigger factors for reactivation are numerous and include physical stimuli such as corneal trauma through injury, surgery and excimer laser[15]. Other factors such as emotional stress, sun exposure and menstruation[16] are also recognised to trigger recurrent disease. The frequency of epithelial HSV recurrence is higher in

patients with diabetes and atopic disease, corneal transplant patients, and immunocompromised individuals[17].

PATHOGENESIS OF HSV INFECTION

HSV in general, can infect a variety of host cells like epithelial cells, fibroblasts, neurons and lymphocytes, thus is regarded as 'broad cell tropic'. The mechanism of viral entry varies depending on the cell type but mainly occurs in two different steps: "In the first step, viral glycoproteins bind to the host cell receptors and in the second step, the viral envelope either fuses with the plasma membrane or undergoes endocytosis. Post fusion, viral nucleocapsid and tegument proteins are released into host cytoplasm, from where the proteins are transported into the nucleus by the dynein-dynactin protein complex. The capsids are propelled through the negative end of microtubules and released into nucleus through nuclear pore complexes. Post infection into nucleus, host RNA polymerase II initiates viral gene expression. HSV genes are expressed in a temporal regulated manner, in three distinct classes: immediate early (IE/a), early (E/β) and late (L/y) genes. A procapsid is assembled inside the nucleus and packaged with viral DNA to form a mature capsid initially fuses with inner nuclear membrane (primary envelopment) to form an enveloped particle and gain fuses with outer nuclear membrane (de-envelopment) to release the capsids into cytoplasm. In the cytoplasm, capsids re-envelope (secondary envelopment), by budding into the Golgi compartment and are finally secreted from the infected cells."[18] (Figure 2)

Infection of the corneal cells with HSV provokes an interaction that induces a cascading immune response, rather than solely a direct cytolysis of corneal cells by the HSV. During HSV corneal infection there is an influx of polymorphonuclear (PMN) leucocytes, macrophages, natural killer cells and Langerhans cells into the underlying corneal stroma[19]. The influx of these immune cells is chemokine dependent. As few animal studies of corneal HSV infection employ recurrent infection models, little is understood about the mechanism of recurrent herpes simplex keratitis (HSK)[19].

The pathogenesis of corneal fibrosis is partly understood. It is thought that recruited inflammatory cells release pro-inflammatory cytokines, chemokines and growth factors that initially aid in virus removal but then cause tissue destruction and scarring[5,8]. Connective tissue in corneal scars is continually persistently remodeled but the lamellar re-organization remains different to that of unwounded corneal tissue[16] leading to increased light scatter and loss of transparency[20].

HERPETIC EPITHELIAL KERATITIS

Corneal epithelium may be involved in up to two-thirds of cases with ocular involvement. In early stages, fine or coarse granular spots form a punctate epithelial keratopathy. Within 12–24 h the cell nuclei become laden with replicating virus and the infected cells swell up prior to releasing the virus into adjacent areas. This process manifests clinically as a painful infection with raised dendritiform lesions that displace fluorescein (negative staining) but stains with rose bengal. Destruction of the basement membrane follows, leading to the formation of a dendritic ulcer with characteristic branching linear pattern with large terminal bulbs and swollen epithelial borders (Figure 3). The base of ulcer stains with fluorescein and the borders, though stain negative with fluorescein, can be demarcated with rose bengal or lissamine green. Around one quarter of cases heal spontaneously. Enlargement of the ulcer may occur, leading to a geographic ulcer in a quarter of patients. Epithelial disease usually resolves but persistent punctate epithelial keratopathy, recurrent corneal erosions or epithelial granularity may be present in the long-term. Also, some degree of anterior stromal reaction is common underlying the epithelial lesions. HSV epithelial keratitis is typically unilateral. The contralateral eye is infrequently affected, either simultaneously or subsequently in healthy individuals[8, 17].

NEUROTROPHIC KERATOPATHY

Sometimes overlooked in HSV keratitis, impairment of corneal sensation develops with loss of corneal lustre and an irregularity of the corneal surface. Punctate epithelial erosions may present and progress to a persistent epithelial defect with shallow smooth borders of grey, elevated, thickened and rolled epithelium, in absence of trauma, infection and desiccation, a condition generally known as neurotrophic keratopathy (NK) [8,21].

The cornea "is the most densely innervated tissue of the body. Its fibers, mostly sensory in origin and derived from the ophthalmic branch of the fifth cranial nerve, enter peripherally parallel to the corneal surface. These nerves lose their myelin sheaths close to the limbus and continue to advance toward the center of the tissue as they subdivide into smaller and more superficial branches. Eventually, a subbasal nerve plexus is formed with nerve endings that penetrate the corneal epithelium. Corneal fibers form the afferent arm of reflexes for blinking and tearing by sensing thermal, mechanical, and chemical stimuli that cause the release of crucial soluble factors for maintenance of wound healing and homeostasis of the ocular surface. Corneal sensory nerves release a variety of biologically active neurochemicals on which the healthy state of the cornea depends. Large numbers of these fibers contain substance P (SP) and/or calcitonin gene-related protein (CGRP), two neuropeptides with described roles in epithelial renewal and wound repair. The integrity of the cornea relies on a competent nerve supply, thus the structural patterns of its nerves, including density, number, degree of branching, and tortuosity, have clinical relevance."[22] Dysfunction of corneal innervation can result to degenerative neurotrophic keratopathy.

Herpetic viral infections of the ocular surface such as HSV are thought to be a major cause of the development of NK characterized by decreased corneal sensation, blink reflex, and tear production as consequence of damage to the sensory fibers innervating the cornea. The cause of corneal nerve degeneration following HSV-1 infection remains unclear but likely involves the immune system and events that transpire within the sensory ganglion. "HSV-1 infection results in a dramatic regression of sensory afferents innervating the cornea, mostly SP and CGRP nociceptive fibers, during acute infection accompanied by the loss of corneal sensitivity. After the viral infection of the tissue has cleared, the cornea reinnervates but often without the normal arrangement of its fibers, peptidergic content, or function. Physiologically relevant concentrations of SP are found in the normal cornea and tears, which have been reported to decrease in patients with herpetic keratitis. A reduction in SP content in HSV keratitis is a result of the profound loss of the sub-basal nerve plexus, associated with reduction of corneal sensation in patients following HSV infection."[22]

The resulting breakdown of corneal epithelium persists and will not heal unless therapeutic measures are taken immediately after diagnosis. If left untreated, corneal scarring, thinning, vascularisation and perforation as well as secondary corneal infection may ensue with detrimental effects to vision and even globe itself. Depending on the severity and stage of the disease, there are several treatment modalities aiming at promoting epithelial cell growth and preventing disruption of the ocular surface. These vary from ocular lubricants, tarsorrhaphy, botulinum toxin-induced ptosis, growth factors and autologous plasma in early to moderate cases and can include collagenase inhibitors, tissue adhesives, conjunctival flaps, amniotic membrane use and penetrating or lamellar keratoplasty in more severe keratopathies; though poor outcomes are expected with the latter modality in severely anaesthetic corneas[8,21,22].

HERPETIC STROMAL KERATITIS

For many years, stromal keratitis was considered to be solely an immune response to epithelial disease. More recently, it has been proposed that the pathogenesis lies in the immune response to HSV invading the anterior stroma, either through viral reactivation of latent HSV in sensory nerves or to the direct spread from epithelial infection[8,23].

Non-necrotising stromal keratitis may occur without history of epithelial keratitis and the epithelium is usually intact. Stromal inflammation may be focal, multifocal or diffuse and there may be an associated anterior uveitis. The inflammation may lead to stromal scarring, thinning, neovascularisation and lipid deposition. Stromal neovascularisation may be sectorial or diffuse and occur in several layers of the cornea. In necrotising stromal keratitis, there is "necrosis, ulceration, and dense infiltration of the stroma usually with an overlying epithelial defect. HSV antigens and HSV DNA are also present in patients with necrotising stromal keratitis. Greyish white homogeneous abscesses with oedema, keratic precipitates, severe iridocyclitis and raised intraocular pressure may develop. Severe inflammatory response may result in a destructive inflammation leading to thinning and perforation especially where there is an associated bacterial infection."[8]

The "pathogenesis of corneal scarring and vascularisation in HSK is still uncertain. One of the major events after HSV-1 infection is the production of proinflammatory cytokines and chemokines and an invasion of the cornea by PMN. This response helps in clearing the virus but at the same time lends entry to various cytokines and angiogenic factors secreted by the PMN. Co-ordinated phenotypic changes, extracellular matrix (ECM) deposition and remodelling are the key elements in the process of tissue repair as in corneal scarring. Various cytokines and growth factors are involved and the most important of these are epidermal growth factor (EGF) and transforming growth factor b (TGFb). Angiogenesis has been demonstrated as early as 24 h post-infection, thereby supporting the role of corneal vascularisation in the severity of HSK. This suggests that HSV infection may disrupt the normal equilibrium

between angiogenic and anti-angiogenic stimuli leading to an "angiogenic switch" initiating angiogenesis. HSV infection can induce the production of many angiogenic factors"[8] such as thrombospondins (TSP) 1 and TSP 2, vascular endothelial growth factor (VEGF), matrix metalloproteinases (MMP) 2 and 9, platelet-derived growth factor (PDGF) and beta fibrosing growth factor (bFGF). "Hypoxia due to corneal oedema may also serve as an angiogenic stimulus. The source of these factors seems to be mainly PMN but VEGF is also expressed in epithelial, endothelial and stromal cells. The angiogenesis cascade likely involves cytokine mediated and other paracrine effects. These findings support the hypothesis of alteration of the normal balance between angiogenic and anti-angiogenic responses as the likely cause of corneal vascularisation in HSK and may form the basis for the next generation treatment options for this condition."[8]

ENDOTHELIITIS AND DISCIFORM KERATITIS

HSV may be associated with endothelial cell inflammation and consequent dysfunction[23]. Herpetic endotheliitis is typically described according to the pattern of endothelial disease: disciform, diffuse or linear[5,8]. Disciform Keratitis is the most common form and is seen as a disc-shaped area of stromal oedema in the central or paracentral cornea. It usually results in full thickness stromal change and the cornea is often described as having a ground glass appearance. Keratic precipitates may be present (Figures 4a-4b). Corneal thickness increases during active endotheliitis due to changes to the Na+/K+-ATPase pump density that regulates ion flux and thus water movement in and out of the cornea[23]. Corneal thickness is increased during the active phase of the disease and tends to normalize as the endotheliitis resolves[23,24]. Stromal inflammation and stromal oedema are often difficult to differentiate.

It is unclear whether endotheliitis is caused by direct cytolytic attack of virus on the corneal endothelium or is the result of the cytokines and other mediators of the immune and inflammatory responses such as prostaglandins, leukotrienes and interleukins. However, literature data does not convincingly document that viral

infection of the endothelium is the cause of the endothelial pathology observed and suggests that physical destruction of the endothelium is not likely to be the cause of oedema[23].

PENETRATING KERATOPLASTY AND HSVK

The recurrence of herpetic disease in the donor cornea following penetrating keratoplasty (PK) is a significant problem and can precipitate corneal transplant rejection[8]. Reported recurrence rates vary but have been documented as high as 27% in the first year[5,8]. The incidence of newly acquired HSV keratitis is 14–fold higher in transplant (PK patients or any transplant patients e.g. renal) patients compared with the normal population[25].

Ocular herpes simplex was the cause of graft failure in 4% of the failed penetrating corneal grafts according to The Australian Corneal Graft Registry[26].

The use of (topical or/and systemic) antivirals following penetrating keratoplasty is supported by several studies and is recommended for at least the first year post-operatively[27,28].

THE HED STUDY

The Herpetic Eye Disease Studies (HEDS) I and II were conducted prior to the availability of newer antiviral agents other than acyclovir but are still serving as guidance for the management of herpetic eye disease. The HED studies validated the use of topical corticosteroids in the treatment of herpes stromal keratitis and assessed the efficacy of oral acyclovir as an adjunct to treatment (Tables 1a-1b) [29, 30, 31, 32].

The HED study I compared patients receiving topical corticosteroid (n = 57) versus a placebo medication (n =49). It was noted that the group treated with corticosteroids had a significantly reduced time to resolution and a risk reduction of 68% of persistent or progressive stromal keratouveitis[30,32]. Topical corticosteroids are routinely used in the treatment of herpetic stromal keratitis.

The HED study I also evaluated effectiveness of oral acyclovir in the management of stromal herpes keratitis. Patients with disciform keratitis and necrotizing stromal keratitis were included. All patients received topical corticosteroid and trifluridine and were randomized to groups receiving oral acyclovir (at treatment dose: 400mg 5 times a day) or a placebo drug. Treatment failure (defined as no improvement, worsening of condition or an adverse event) was observed earlier, at 62 days, in the placebo group compared to the acyclovir group – where treatment failure occurred on average at 84 days. Additionally, visual acuity improvement was greater in the patients in the acyclovir group compared to the placebo group over the course of 6 months. However, these results were not statistically significant and the use of oral acyclovir as an adjunct to topical steroid therapy remains controversial[30,31]. Despite this, acyclovir is often used alongside topical steroid therapy in the treatment of stromal keratitis.

Another part of the HEDS I was to look into the benefit of adding oral acyclovir to a regimen of topical prednisolone phosphate and trifluridine for the treatment of HSV iridocyclitis. Treatment failure occurred in 50% of the 22 patients in the acyclovir-treated group and in 68% of the 28 patients in the placebo group. Although the results of this study were not statistically conclusive because of the small number of patients, they suggested that there is benefit of oral acyclovir in the treatment of HSV iridocyclitis[30].

With regard to disease recurrence, the HED study II found that oral acyclovir prophylaxis at a low dose (400mg twice a day), significantly reduced HSV recurrence rates compared to placebo and was particularly important to the subgroup of patient with a previous history of HSV stromal keratitis[29,30]. In addition, HEDS II found no additional benefit of oral acyclovir in preventing HSV stromal keratitis or iritis when added to topical trifluridine in cases of HSV epithelial keratitis[30]. Finally, the same study looked into the role of external or behavioral factors on ocular recurrences of HSV infections concluding that no such an association exists[33].

USE OF SYSTEMIC ANTI-VIRAL MEDICATION IN HERPETIC EYE DISEASE

The use of an antiviral therapy for the prevention of recurrent episodes of HSK has been supported by clinical research and is centered on acyclovir. Research into the clinical effectiveness of other agents, such as valacyclovir, is limited. In terms of pharmacokinetics and drug safety profiling valacyclovir is well absorbed, has good systemic bioavailability and a good safety profile[34]. In a trial conducted by Weller et at, found an excellent safety profile when increasing doses of valacyclovir were administered[35]. There were few reported cases of gastrointestinal upset and headaches[27]. Unfortunately, there is insufficient clinical research to determine a difference in clinical effectiveness between acyclovir and modified acyclovir antivirals. There are, however, both animal and human studies that suggest that valacyclovir can be used as a comparable alternative to both topical as well as intravenous acyclovir[34,36,37]. Valacyclovir requires a reduced frequency of administration, and hence may impact on adherence to medication.

The HED study was a multi-centered, randomized, placebo-controlled trial and has formed the foundation for the management of herpetic eye disease particularly stromal keratitis (see table 1)[29,30,31,32]. Although there is no curative treatment for HSV infection and its elimination from the nervous system has not yet been possible, treatments are aimed at reducing corneal scarring and maintaining viral latency[30]. The HED study, found that patients treated with prophylactic oral acyclovir (400 mg twice a day) had a recurrence rate of HSVK of 19% compared with 32% in individuals treated with placebo[30]. As mentioned previously, the results of the HED study were published in 1994[31], prior to the availability of newer acyclovir analogues such as valacyclovir that are currently thought to be more effective. To date there remains no randomized controlled trial examining the effectiveness of valacyclovir.

PHARMACOKINETICS

Acyclovir is nucleocide analogue that is selectively phosphorylated by the thymidine kinase (TK) of the HSV and herpes zoster virus (VZV)[38]. Acyclovir is also active, but to a lesser extent, against Epstein-Barr virus and cytomegalovirus[34]. It inhibits viral replication by acting as a substrate for DNA polymerase resulting in chain termination and preventing further elongation of the viral DNA chain[38,39]. Acyclovir is highly specific for herpes virus infected cells and is known to be effective in the treatment of active herpes infection - both herpes simplex and herpes zoster- and in the suppression of latent disease[38]. The DNA polymerase of herpes simplex virus has a 10- to 30-fold greater affinity for acyclovir triphosphate than that of uninfected cells[40]. Acyclovir is only partially absorbed by the human gastrointestinal tract. Peak plasma concentrations are achieved approximately 1.5 hours after oral ingestion and have a half-life of 2-3 hours[41]. The bioavailability at therapeutic doses is limited at 20% and because of this, it needs to be to be administered in high doses and at high frequency[42,43].

Valacyclovir is the l-valyl ester of acyclovir. It is synthesized by the addition of an amino acid, L-valine, to the acyclovir molecule (Figures 5a-5b)[38]. It serves as a pro-drug as it is rapidly converted to acyclovir and l-valine. The conversion of valacyclovir to acyclovir leads to an increased acyclovir bioavailability by 3-5 fold compared to oral acyclovir administration[36]. Unlike acyclovir which reaches a bioavailability of 10-20% due to its low absorption, acyclovir bioavailability after valacyclovir administration increases to more than 50%.[36] Maximum plasma concentration of acyclovir was seen after 2 hours of oral administration[41]. Studies comparing acyclovir and valacyclovir dosing found that in order to achieve a dose equivalent to 800mg of acyclovir 5 times a day, the treatment dose for herpes zoster infections, a dose of 500 mg twice a day or 250mg of valacyclovir 4 times a day would have to be administered[41]. Additionally, good drug delivery is achieved with valacyclovir, as it is almost fully converted to acyclovir during first pass metabolism; studies measuring valacyclovir concentrations in 24 hour urine collection estimated a loss of 1% unchanged valacyclovir[41].

Studies with human gastrointestinal cell lines demonstrated an increase in mucosal to serosal transport of valacyclovir compared to acyclovir, suggesting a carrier-mediated transport[35]. After the absorption of valacyclovir, the L-valine moiety is hydrolyzed to yield acyclovir. The metabolism of valacyclovir to acyclovir is thought to occur in the gut lumen (Figure 6). The increased uptake and rapid hydrolysis results in a greater systemic acyclovir concentration. It has been reported that more than 95% of valacyclovir is converted to acyclovir[35]. Studies comparing the bioavailability of acyclovir after the administration of 1g dose of valacyclovir versus acyclovir showed this to be 54.2% and 15-30% respectively[35]. The high bioavailability of valacyclovir leads to plasma acyclovir levels comparable to those obtained with intravenous administration of acyclovir. Weller and associates found that 1000 mg of valacyclovir given four times a day resulted in equivalent acyclovir levels to intravenous acyclovir administration at doses of 5mg/kg every 8 hours. Higher plasma levels comparable to intravenous doses of 10 mg/kg every eight hours can be achieved with higher doses of valacyclovir such as 2000 mg four times a day[35].

SAFETY PROFILE OF ORAL ANTIVIRALS

Valacyclovir and acyclovir are well-tolerated drugs. The most commonly reported side effect is nausea, vomiting, headache and gastro-intestinal upset. Dosage modification is required in patients with renal impairment as there is a risk of nephrotoxicity[34]. It has been suggested that the lower peak plasma concentrations associated with oral valacyclovir treatment may reduce the risk of renal side-effects compared to acyclovir[44].

ANIMAL MODELS IN HSVK

Animal models have been used to study the pathogenesis of HSVK and to test the effects and efficacy of novel therapies, although it is recognized that there may be significant limitations in extrapolating findings of these studies to humans[11].
Asbell examined the recurrence rate of HSVK in rabbits after undergoing excimer laser photokeratectomy and also studied the recurrence rates in rabbits treated with different doses of valacyclovir[16]. It was reported that excimer laser photokeratectomy was a triggering factor for HSVK reactivation and a recurrence rate of 67% was observed[16]. Most importantly, this study found that reactivation rates were reduced in the valacyclovir treated group of rabbits and that the recurrence rates of disease were further reduced with increased drug doses[16]. More specifically, 50mg/kg per day of valacyclovir reduced recurrence rates to 50% and a dose of 100mg/kg of Valacyclovir per day reduced recurrence rates further to 17%. With a dose of 150mg/kg of valacyclovir per day, no disease recurrences were observed[16].
Kumar et al showed that HSV-1 DNA shedding in rabbit tears decreased with increasing doses of valacyclovir. However, doses greater than the human equivalent to 500mg valacyclovir OD were needed to suppress DNA shedding[44].
In a study performed in New Zealand Albino rabbits, Dias et al showed that acyclovir can be detected in the aqueous humor following intravenous acyclovir and valacyclovir administration[45].

HUMAN STUDIES

Prior to the advent of antivirals use in HSK, the mainstay of treatment involved to rub off the infected surface of the eye. Various methods of curettage, cauterisation, and chemoablation were used to remove the corneal epithelium. Potential shortcomings of debridement included damage to Bowman's layer and exacerbation of corneal inflammation and opacification. Epithelial keratitis recurred after debridement, presumably due to viral shedding or infection of remaining cells of the ocular surface. With the continuous emergence of the various antivirals, using a

wiping method followed by an antiviral drug is not consistently better than just an antiviral medication. Compared to topical antiviral monotherapy, the combination of an antiviral agent with debridement has inconsistent effects on enhancing healing and improving outcomes[46].

The efficacy of prophylactic valacyclovir in the prevention of HSV ocular recurrences was compared to that of acyclovir by Miserocchi el al[47]. He compared 26 immunocompetent patients in two treatment groups measuring disease recurrence over a 12-month period. Disease recurrence was 23.1% in both groups and there was no discrepancy in disease severity, frequency and adverse events[47]. He concluded that 500mg of Valacyclovir once a day was as effective as 400mg of acyclovir twice a day in preventing disease recurrence[47].
Sozen et al in 2006 conducted a study of 28 patients with epithelial HSVK[48]. He noted that patients treated with valacyclovir (1gr twice a day) instead of acyclovir ointment (five times a day) healed faster[48].

Higaki et al advocated the use of valacyclovir in patients intolerant to topical acyclovir and also observed that HSV DNA was undetectable after a week of treatment and coincided with healed epithelial disease[36].

In a study looking at the ocular penetration of acyclovir after oral valacyclovir and intravenous acyclovir administration, Huynh et al found that orally administered valacyclovir quickly leads to substantial vitreous acyclovir concentrations in non-inflamed human eyes[49]. It was reported that on average, the vitreous acyclovir levels were approximately 25% that of the serum levels. The time to maximum serum concentration of acyclovir after an oral dose of valacyclovir has been estimated at 2 hours[49].

HSV ANTIVIRAL RESISTANCE

"Among immunocompetent patients, resistance to ACV is rare. Several reports have described prevalence below 1% in this population whereas prevalence of ACV resistance among immunocompromised patients is about 5%. According to the literature, most ACV-resistant HSV isolated from immunocompetent individuals have been detected in the course of recurrent genital herpes. In this situation, the observed prevalence ranged from 3.5 to 8.6%. Concerning orofacial herpes infections, a recent study reported one case of ACV resistance in 924 HSV isolated from subjects with recurrent herpes labialis, corresponding to a prevalence of 0.11%. Three mechanisms may be involved in HSV resistance to ACV: a loss of thymidine kinase activity (TK deficient virus), an alteration of TK substrate specificity (TK altered virus) and/or an alteration of DNA polymerase activity. Mutations occurring in the viral gene encoding TK are the most frequent and 95% of ACV-resistant isolates present a TK deficient phenotype[50].

Foscarnet and cidofovir act directly on viral DNA polymerase without previous activation by viral TK and both these molecules are active on viruses resistant to ACV because of a mutation in the TK gene. However, in clinical practice, they may be associated with significant toxicity. Another way to manage ACV resistant HSV infection is to improve the immune status of the patient, where possible, by modifying immunosuppressive treatments."[50] Significant advances have been made towards the design and development of novel antiviral therapeutics during the last decade. Pharmaceutical companies are moving forward with several new compounds into various phases of clinical trials. The development of new therapeutic agents with intrinsic antiviral activities and novel mechanism of action, superior efficacy and less potential for adverse effects is essential. The newly developed drugs could be used not only as monotherapy but also potentially in combination with other antivirals[18, 39, 50].

TOPICAL ANTIVIRALS IN HERPETIC EYE DISEASE

Early generation drugs

The topical antiviral agents used against HSV have primarily been nucleoside analogues. They interrupt viral DNA synthesis by the irreversible binding of viral DNA polymerase within infected cells[51,52].

Early generation drugs included idoxuridine, iododesoxycytidine, vidarabine, and trifluridine. All of these drugs were effective in HSV keratitis but they also exhibited non-selective activity against DNA synthesis by inhibiting DNA replication of both normal and viral-infected cells; thus, resulting in cellular and ocular surface toxicity such as epithelial keratitis, ulceration, delayed wound healing, follicular and cicatricial conjunctivitis as well as punctal and canalicular stenosis. They also tended to have low bioavailability and as a result their use was limited as more effective and better-tolerated topical medications became available. However, "trifluridine, a synthetic pyrimidine nucleoside, was approved by the United States (US) Food and Drug Administration (FDA) as a 1% solution for treatment of HSV keratitis in 1980. It is administered every 2 hours, up to nine times a day and has become the most widely used topical antiviral agent for treatment of HSV keratitis in the US."[50] It was the only topical antiviral medication used in the HED studies despite the local toxic side effects that accompany its use.

"Acyclovir is another purine nucleoside analogue, but with selective inhibitory activity against HSV DNA polymerase. It is able to inhibit viral DNA synthesis without concomitantly interrupting uninfected host cells."[51] In Europe, acyclovir is available as a 3% ointment and it has become the first-line topical treatment for HSV epithelial keratitis in Europe and elsewhere outside of the US. It is used five times daily in the acute phase and it has been demonstrated to be effective against HSV keratitis. Local toxicity is less than that of the nonselective agents mentioned earlier but the ointment contains vaseline and can cause some discomfort and blurred vision, which may affect patient compliance. Acyclovir is poorly soluble in water and it requires formulation in a polyethylene glycol base[51,52].

A few side-effects has been linked to the topical use of Acyclovir with superficial punctate epithelial erosions being the commonest (9.8%) followed by burning or stinging on application of the ointment (4%)[53].

In order to compare the effectiveness of oral and topical acyclovir a study of sixty patients with simple dendritic corneal ulceration was conducted by Collum et al. The patients "were randomly assigned to double blind treatment with either acyclovir tablets (400 mg) or acyclovir ophthalmic ointment administered five times daily. There was no significant difference in the proportions of patients healed in either treatment group (88.9% on oral acyclovir and 96.6% on acyclovir ointment). The median healing time was five days in both groups. No systemic or significant local side effects were noted in either treatment group."[54] The study concluded that "oral administration of acyclovir (400 mg, five times daily) may be an effective alternative to topical therapy in selected patients."[54]

Ganciclovir: the new generation

"Ganciclovir, like acyclovir, is a synthetic purine nucleoside, an analogue of guanosine (Figure 7) and has a broad spectrum of activity against a variety of viruses, including all human herpes viruses (HSV-1, HSV-2, varicella-zoster virus, Epstein-Barr virus, CMV, and human herpesvirus 6) and adenovirus."[51] It is used intraocularly and systemically for the management of CMV related sight- and life-threatening complications respectively.

Ganciclovir is phosphorylated by viral thymidine kinases into ganciclovir monophosphate. "Within virus-infected cells, both viral and cellular thymidine kinases catalyze further phosphorylation of ganciclovir monophosphate into ganciclovir triphosphate, the active metabolite. Ganciclovir triphosphate accumulates in virus-infected host cells, interfering with viral replication in two ways: 1) by direct incorporation into viral DNA, inducing single- and double-strand breaks, resulting in viral DNA chain termination;"[51] and 2) by competitive inhibition of viral DNA-polymerase, "interrupting new viral DNA synthesis. Ganciclovir's potent effects are irreversible with the HSV-infected cells becoming rapidly apoptotic, resulting in cell

death. Ganciclovir is not recognized as a substrate by human thymidine kinase within healthy human cells and the active metabolite does not build up in uninfected cells."[51] Consequently, while strongly inhibiting viral replication in cells infected with HSV, it does not have an effect on the DNA of healthy cells resulting in less host toxicity[51,52].

"Ganciclovir is now approved as a topical antiviral agent for treatment of acute herpes simplex epithelial dendritic ulcerative keratitis, in the form of a 0.15% aqueous gel. It is marketed in Europe under the trade name Virgan® (Spectrum Théa Pharmaceuticals, Macclesfield, UK) and in the US as Zirgan® (Bausch and Lomb Incorporated, Rochester, NY, USA). Each gram of the gel contains 1.5 mg of active ganciclovir in a hydrophilic polymer base."[51] It is used five times per day until the corneal ulcer heals, then one drop three times a day for 7 additional days. Ganciclovir 0.15% ophthalmic preparation was found to be both safe and equally effective to acyclovir, however it has been postulated that ganciclovir resistance is much more rarely encountered and thus it could be used as an alternative in acyclovir-resistant cases; the topical formulation is well tolerated, nontoxic to the ocular surface, which could also be attributed to the hydrophilic nature of its formulation, and does not cause adverse systemic side effects. The most common adverse and toxic side effects are blurred vision, eye irritation, punctate keratitis, and conjunctival hyperemia and occur much less frequently compared with acyclovir[51,52].

Ocular pharmacokinetics

Topical acyclovir and ganciclovir "demonstrate effective penetration through the cornea to achieve therapeutic levels in deeper structures and the aqueous humor. Its hydrophilic base allows ganciclovir to be solubilized as an aqueous gel. This enhances drug resorption, permitting equivalent therapeutic effects at far lower concentrations than that of acyclovir 3% ointment."[51]

A single drop of ganciclovir gel on the ocular surface can produce tissue concentrations higher than the effective concentrations for HSV-1 and HSV-2 for over 4 hours. "This capacity to concentrate in ocular tissues and fluids could be related to continuous drug absorption over time because the gel formulation permits extended drug contact on the ocular surface. Ganciclovir gel has often been described as "galenic"," [51] a term used for a medication designed with maximal absorption properties.

Ganciclovir molecule is relatively small-sized with high lipophilicity and high cellular affinity. Increased lipophilicity enhances permeability through the corneal epithelium and the presence of an epithelial defect enhances corneal absorption by eliminating one of the primary barriers to absorption[51].

CONCLUSION

Herpes simplex keratitis is an important cause of visual impairment and the pathogenesis of the different disease moieties remains elusive.
Current therapeutic practice remains founded upon the outcomes reported by the HEDS, the first large, randomized controlled study into the treatment of HSVK. Newer medications such as valacyclovir however, which appears to have a superior therapeutic effect compared with acyclovir may provide a realistic treatment alternative for the future. The reduced frequency of dosage may aid compliance and the increased bioavailability may increase efficacy although the higher cost of valacyclovir may present a barrier to its use.

The "increasing use of ACV, especially in prophylaxis treatments among transplanted patients, has raised the fear of an increasing incidence of ACV-resistant infections. Recent survey studies have shown that this is not the case and that ACV resistance is mainly a concern for severely immunocompromised patients, such as those transplanted with bone marrow from allogeneic origin. Notably, when managing ACV-resistant infections other antiviral drugs with different mechanisms of action may be used, such as foscarnet and cidofovir."[50] However, there is still increasing

need, and research is ongoing, to develop new anti-herpetic compounds with different mechanisms of action which will be safe and effective against emerging drug-resistant viral strains.

In addition, "based on safety, efficacy, and tolerability, ganciclovir gel 0.15% is now considered the front-line topical antiviral drug for the treatment of dendritic herpes simplex epithelial keratitis. It exhibits less toxicity and offers a simpler dosing regimen than one of the main topical alternatives: trifluridine."[51]
The American Academy of Ophthalmology supports the use of ganciclovir over topical acyclovir ointment despite similar healing rates. This appears to be linked to ganciclovir gel's favorable side effect and tolerability profile. Furthermore, the difference in cost between the two topical agents may influence the choice of treatment[55].

Based on our clinical experience and information in literature we propose an algorithm for the treatment of HSV in its different clinical presentations (Table 2). Clinician's preference and cost issues could potentially affect the decision for the type of treatment[56].

There are several potential topics of interest for future research such as ganciclovir gel's usefulness against HSV geographic ulcers, necrotizing keratitis and iridocyclitis. Additionally, topical ganciclovir could be effective in adenoviral keratoconjunctivitis, CMV keratitis including endotheliitis, and herpes zoster ophthalmicus pseudodendritic keratitis. The clinical potential for this most recently developed topical antiviral agent, therefore, needs to be ascertained[51].

Furthering the understanding of herpetic eye disease and promoting the development of more targeted therapy will undoubtedly alter our practice in the future and reduce the significant disease burden associated with this condition. Finally, redesigning a new, third HED study, comparing various topical and oral antiviral agents could determine the optimal treatment regimen for herpetic eye disease with greater precision and concomitant generation of new information.

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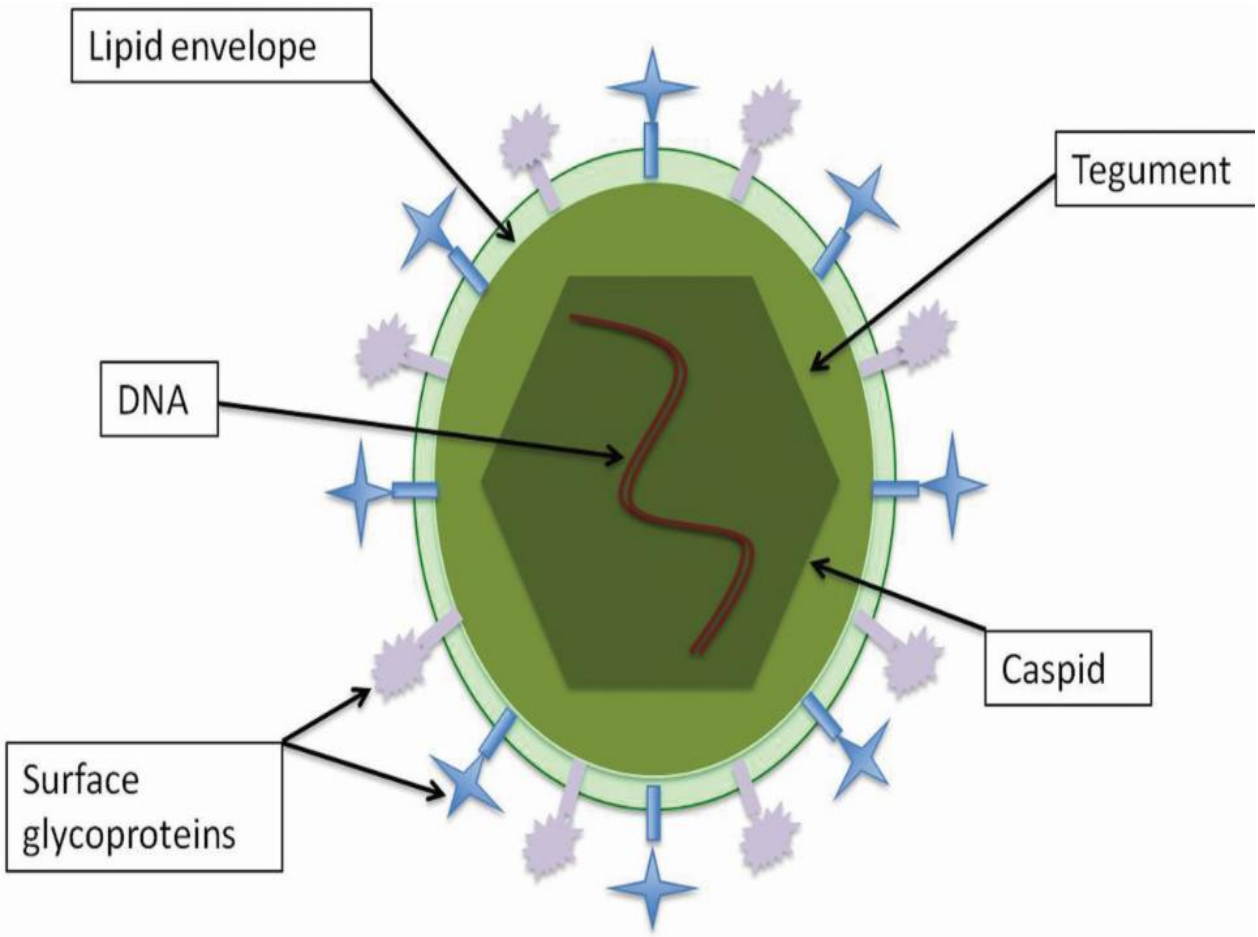


Figure 1: Schematic representation of the HSV-1 virion.

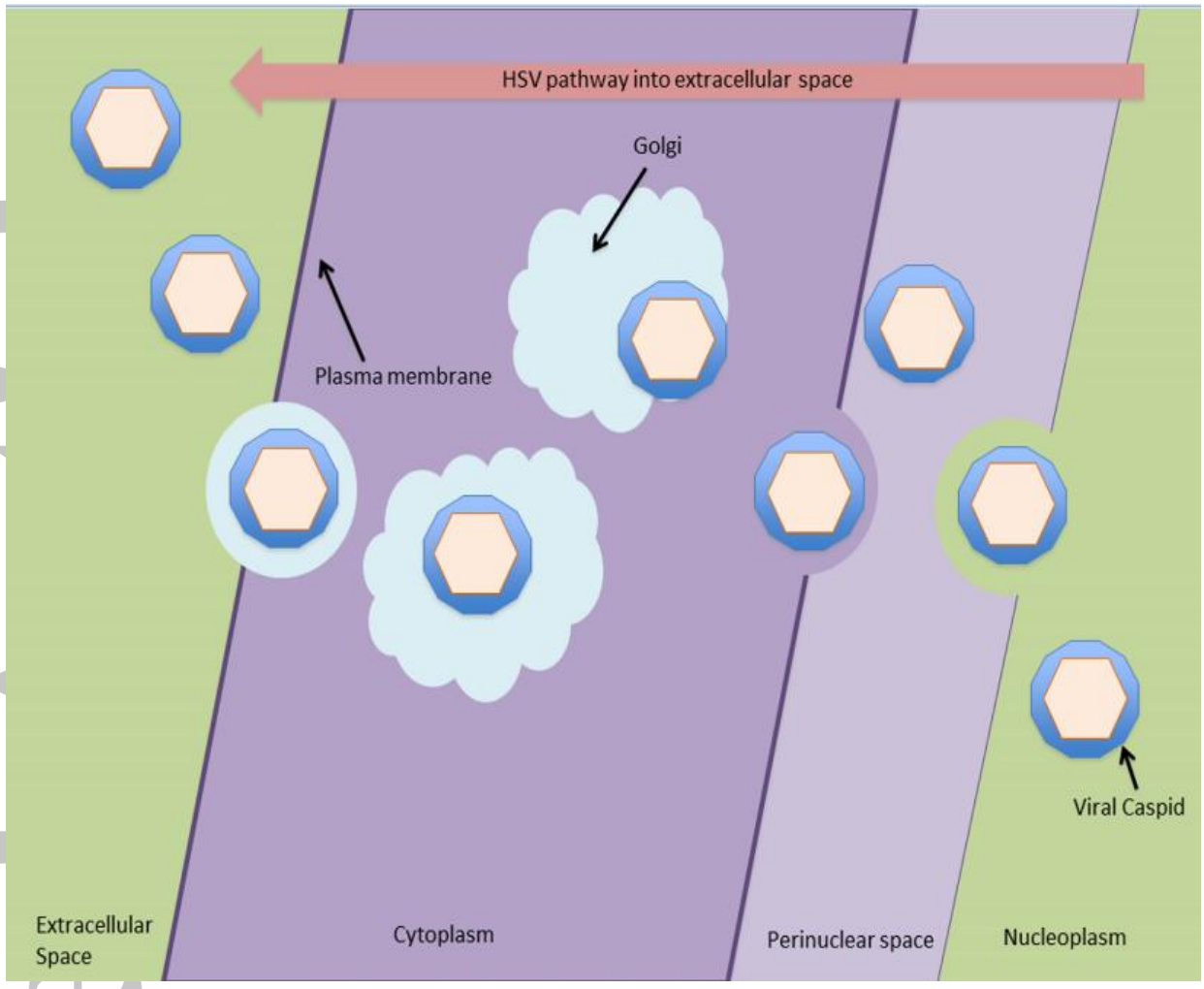


Figure 2: Egress of the HSV virus from the infected cell.

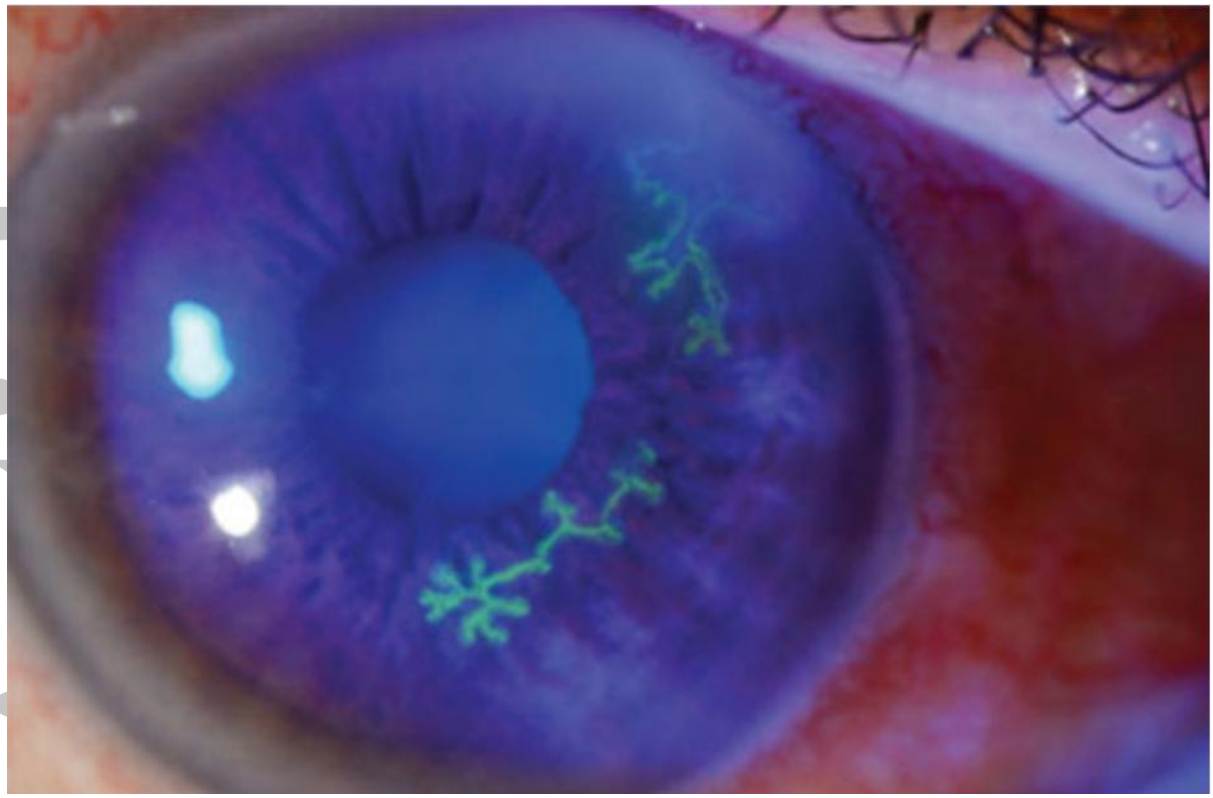
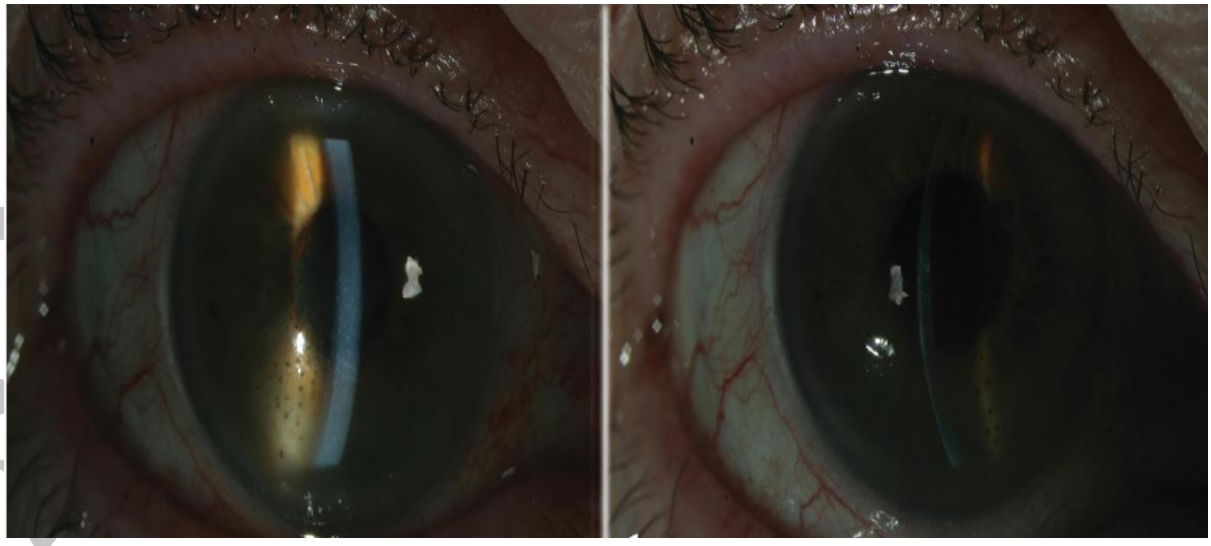


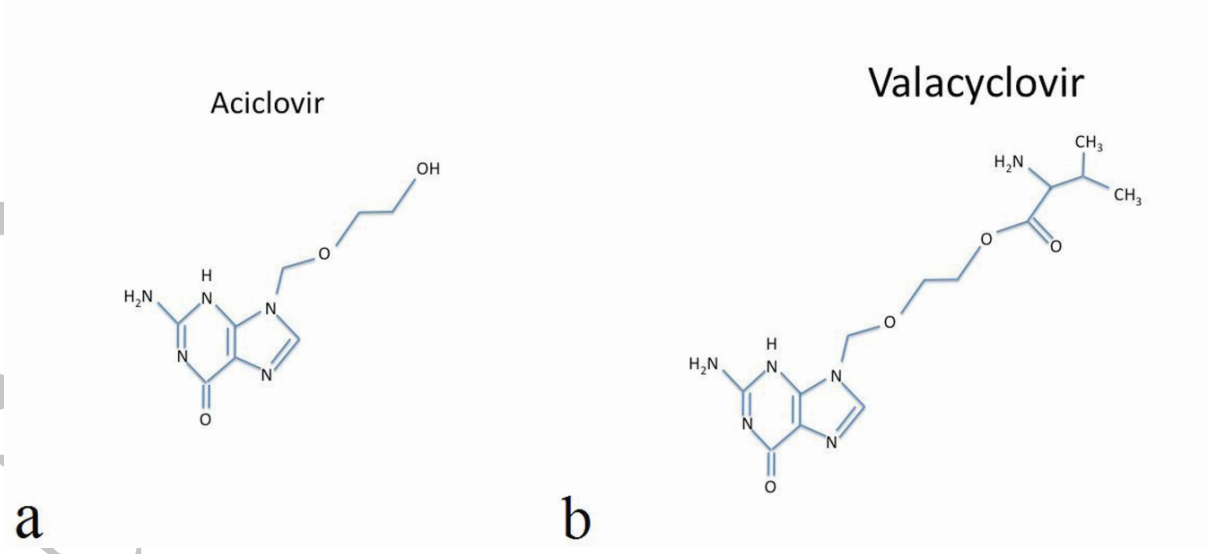
Figure 3: HSV epithelial keratitis with dendritiform pattern of the ulceration stained with fluorescein.



Figures 4a-4b: Endotheliitis and disciform keratitis.

a. Mutton-fat keratic precipitates clearly seen on the corneal endothelium, pigmented in this case, and indicating typical granulomatous herpetic inflammation.

b. oedematous cloudy cornea with increased stromal thickness depicted with thin slit beam, corresponding to the area of the corneal deposits.



Figures 5a-5b: The molecular structure of (**a)** Acyclovir and (**b)** Valacyclovir.

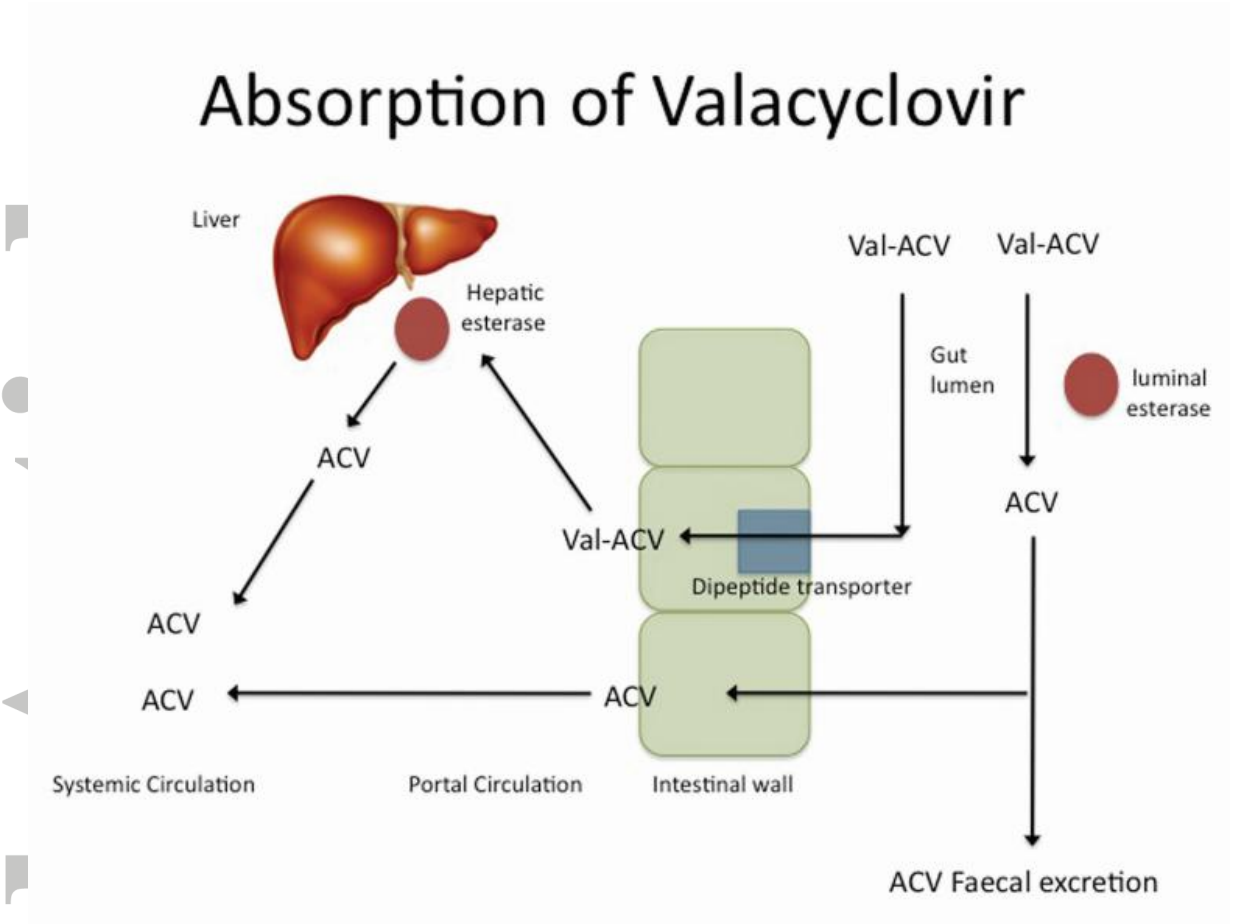
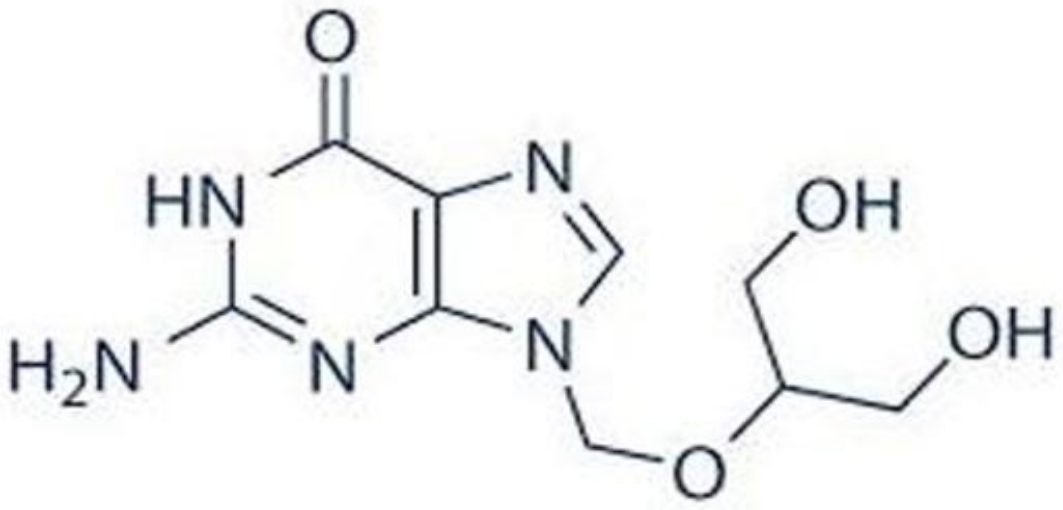


Figure 6: The pharmacokinetics of Acyclovir (ACV) and Valacyclovir (Val-ACV). Oral administration of Valacyclovir yields systemic acyclovir through uptake by dipeptide transporters in the gut lumen and hydrolysis by esterases present in the gut lumen, intestinal wall and liver.



b

Figure 7: The molecular structure of Ganciclovir.

Table 1a:

HEDS	To evaluate the efficacy of topical corticosteroids in treating herpes simplex stromal keratitis in conjunction with topical trifluridine	→	There was faster resolution of stromal keratitis and fewer treatment failures with prednisolone phosphate therapy. Delay of initiation of corticosteroids did not affect eventual visual outcome
	To evaluate the efficacy of oral acyclovir in treating herpes simplex stromal keratitis in patients receiving concomitant topical corticosteroids and trifluridine	→	There was no statistically or clinically significant beneficial effect of oral acyclovir in treating HSV stromal keratitis in patients receiving concomitant topical corticosteroids and trifluridine. Oral acyclovir did not significantly delay the time to treatment failure, decrease the proportion of patients who failed treatment, increase the proportion of patients whose keratitis resolved, decrease the time to resolution, or increase best-corrected visual acuity
	To evaluate the efficacy of oral acyclovir in treating herpes simplex iridocyclitis in conjunction with treatment with topical corticosteroids and trifluridine	→	Treatment failures occurred at a higher rate in the placebo group compared to the acyclovir group but the trial was too small to be statistically significant. Benefit of adding

Table 1b:

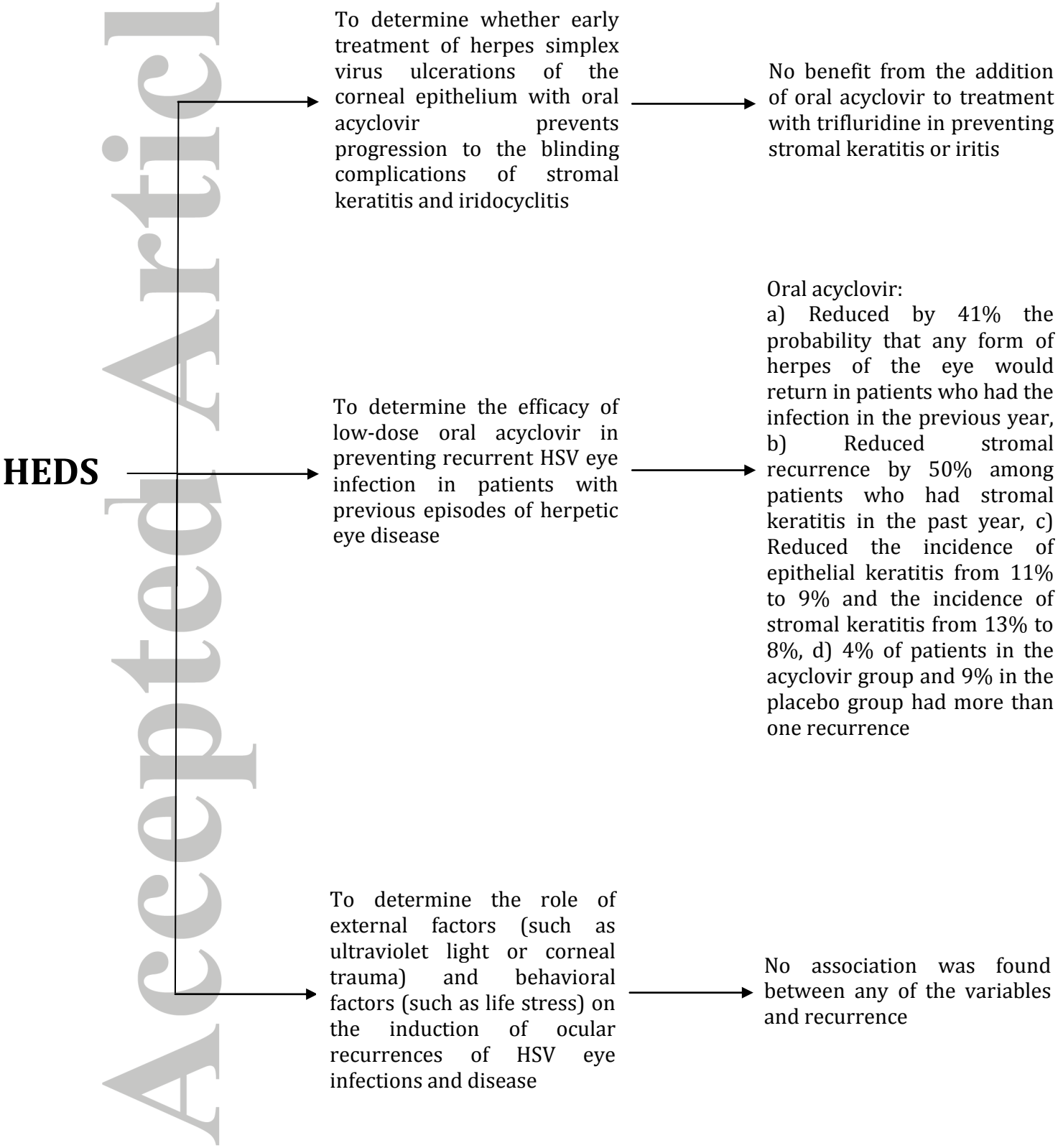


Table 2: Herpes simplex virus keratitis treatment algorithm.

Treatment type / Disease type	**Primary treatment**	**Complementary treatment**	**Potentially beneficial**
Epithelial keratitis	Topical antivirals	Oral antivirals	Debridement Interferon
Stromal Keratitis (Necrotising and non-necrotising)	Topical corticosteroids	Oral antivirals	Topical antivirals Topical cyclosporine
Disciform/ Endothelial keratitis	Topical corticosteroids	Oral antivirals if iritis present and for recurrence prevention	Topical antivirals
Neurotrophic keratitis	Artificial tears Collagenase inhibitors Autologous serum Antibiotics if infected	Surgery Botulinum toxin	Growth factors