Herpetic Keratitis: A review of the evidence

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Introduction

Herpetic eye disease remains a major cause of corneal blindness, with an estimated incidence between 5.9 to 20 /10^5 of the population per year, with a prevalence of approximately 149/10^5 individuals in developed countries. Of the eight herpes viruses known to infect humans, only five cause significant ocular disease and include herpes simplex types I and II, varicella zoster, cytomegalovirus and Epstein-Barr virus (Table 1). Humans are the only known reservoir for HSV and although its epidemiology has changed, it is generally accepted that its prevalence increases with age and can be identified in the trigeminal ganglia of over 90% of the population 60 years or older.

Pathogenesis

Primary infection occurs often during childhood after contact with infected skin lesions, saliva (HSV-1) or genital secretions (HSV-2) of a shedding carrier. Although usually asymptomatic, up to 6% may present with oropharyngeal lesions, characteristic of HSV. Rarely is the eye involved but primary lesions typically evolve rapidly spreading dendrites or geographic ulcers of the corneal epithelium. It is from the trigeminal ganglia that the virus is released. Following initial infection, HSV establishes lifelong latency in the trigeminal ganglia. Initial ocular episodes generally happen much later in life characterized by the classical dendritic ulceration. Upon reactivation, virus travels in retrograde fashion through the nerve axon to provoke new lesions.

In contrast to primary infection, recurrent disease appears in the context of a hypersensitive immune response. However limited to the corneal epithelium, in most cases the immune reaction causes variable degrees of stromal edema. Studies suggest that approximately 10 % of patients with epithelial keratitis will eventually experience stromal disease. It is the stromal disease that may affect vision the most and is the most difficult to treat.

Table 1. Herpesvirus associated with ophthalmic manifestations

<table>
<thead>
<tr>
<th>Virus</th>
<th>Ophthalmic manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herpes simplex virus 1 (HSV-1)</td>
<td>Blepharitis, conjunctivitis, keratitis, anterior uveitis, retinal necrosis (a combination of the above)</td>
</tr>
<tr>
<td>Herpes simplex virus 2 (HSV-2)</td>
<td>Same as above</td>
</tr>
<tr>
<td>Varicella zoster virus (VZV)</td>
<td>Same as above</td>
</tr>
<tr>
<td>Epstein-Barr virus (EBV)</td>
<td>Epithelial and stromal keratitis</td>
</tr>
<tr>
<td>Cytomegalovirus (CMV)</td>
<td>Epithelial and stromal keratitis, endothelitis, and retinitis (or a combination of the above)</td>
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Figure 1. Flourecine staining of a dendritic corneal ulcer.

Figure 2. Rose Bengal staining of a geographic corneal ulcer.
Presentation

The great majority presents unilaterally, with bilateral disease being more common in immunocompromised patients.7

Blepharo-conjunctivitis: It can happen either in the primary infection or as a recurrent disease. Lesions are characteristic, with small vesicles appearing over the eyelid, usually accompanied by edema and moderate pain. In the conjunctiva, it can cause a follicular reaction; occasionally conjunctival dendrites can be identified.8

Epithelial keratitis: Early in disease, clear and raised small vesicles can be identified. As the disease evolves, they coalesce and ulcerate to form the characteristic branching dendrite with raised edges and terminal bulbs containing live virus (Figure 1).4 A geographic ulcer can appear in the setting of topical steroid treatment and immunocompromised individuals (Figure 2).6 Marginal ulcerative keratitis is another form of epithelial disease, usually associated with stromal infiltrate with significantly more pain and increased treatment failure rates (Figure 3). Repeated episodes of inflammation may scar the cornea and decrease its sensitivity, leading to neurotrophic keratopathy.9

Stromal Keratitis: Primary stromal disease can be divided into distinct categories that may have overlapping features. Immune stromal keratitis is the consequence of antigen-antibody response and appears as uni or multifocal stromal edema and haze with or without neovascularisation (Figure 4).4 As inflammation diminishes, scarring is the rule. Necrotizing stromal keratitis is a rare but fulminant manifestation of HSV, appearing as a dense area of suppurative ulcerative keratitis, with a greyish to white stromal abscess, corneal edema, keratic precipitates, severe iridociclitis and raised intraocular pressure. The intense inflammatory response may lead to corneal thinning and perforation. This form of stromal disease is due to direct viral invasion and inflammation.5 Stromal diseases accounts for 2% of initial presentations and 20 to 50% of recurrent herpetic keratitis.5

Endothelitis: Endothelitis is thought to be an immunologically mediated manifestation or herpetic eye disease. It reveals itself as keratic precipitates associated with stromal edema and anterior uveitis in various degrees. Three different forms have been identified: disciform, diffuse and linear. Disciform disease is the most common and is seen as a disc shaped area or stromal edema, diffuse and linear disease is much less common.5

Iridociclitis: This manifestation may appear alone or in conjunction with corneal disease and findings may include anterior chamber inflammation with fine cell keratic precipitates and raised intraocular pressure.9

Diagnosis

Diagnosis is based on clinical findings, although laboratory tests are indicated when the clinical diagnosis is ambiguous. Viral culture remains the gold standard, however it is still unavailable for most clinical settings. Viral antigen and PCR can be useful in certain cases of epithelial keratitis.10

Treatment

Drugs are directed to interrupt viral replication without disturbing the host cellular metabolism and while interfering with key steps such viral adsorption, penetration, uncoating, transcription and synthesis and release of viral proteins.11 The host cellular machinery directed by virus specific proteins does transcription. Crucial proteins in these processes are the thymidine kinase and DNA polymerase, which are virus specific.12

Agents

Trifluridine is pyrimidine nucleoside analogue, that non-specifically inhibits viral and cellular thymidilate synthetase blocking DNA thymidine uptake.11

Acyclovir on the other hand is a synthetic purine nucleoside that is converted to acyclovir monophosphate by the virus-encoded enzyme thymidine kinase and to acyclovir triphosphate by host enzymes. Acyclovir triphosphate is a preferential substrate for viral thymidine, therefore provoking DNA chain termination.12

Valacyclovir (1-valine ester of acyclovir) is pro-drug of acyclovir with increased bioavailability (5 times more).13 Famiclovir is an acyclic guanine derivative, an oral prodrug that is converted by first pass metabolism to penciclovir.14 Penciclovir triphosphate then preferentially inhibits viral DNA polymerase. Compared to acyclovir it has lower affinity for viral DNA polymerase but has a longer intracellular half-life. It is active against HSV-1, HSV-2, VZV and EBV.15,16 Gancyclovir and its produg valgancyclovir are in a synthetic analogues of 2-deoxyguanosine (acyclic purine nucleoside). Ganciclovir triphosphate is a competitive inhibitor of deoxyguanosine triphosphate incorporation into DNA and preferentially inhibits viral DNA polymerases more than cellular DNA polymerases.13,16 In addition, ganciclovir triphosphate serves as a poor substrate for chain elongation, disrupting viral DNA synthesis by a second route.

Vidarabine is an analogue of adenosine.15 This results in the prevention of DNA synthesis, as phosphodiester bridges can longer to be built, destabilizing the strand. Vidarabine triphosphate (Ara-ATP) also inhibits RNA poladenylation preventing transmethylation reactions.17 Vidarabine is more toxic and less metabolically stable than many of the other current antivirals such as acyclovir and ganciclovir.15

Interferons (IFNs) are glycoproteins made and released by host cells in response to the presence of pathogens. Interferons are named after their ability to “interfere” with viral replication within host cells but have other functions: they activate immune cells, such as natural killer cells and macrophages; they increase recognition of infection or tumour cells by up-regulating antigen presentation; and they increase the ability of uninfected host cells to resist new infection.18 By interacting
with their specific receptors, IFNs activate signal transducers and activators of transcription (STAT) complexes; STATs are a family of transcription factors that regulate the expression of certain immune system genes through the Janus kinase-STAT (JAK-STAT) signalling pathway and several other signalling cascades.\textsuperscript{15,19}

Herpetic Epithelial keratitis

Most cases resolve spontaneously within the first three weeks. The rational for treatment is to lessen discomfort, decrease duration and to diminish stromal damage and scarring. Gentle epithelial debridement may be performed to accelerate healing.

Several systematic reviews have recently analysed the available treatments for epithelial herpetic disease.\textsuperscript{18} In general, all available antivirals topical or oral are better than placebo and are thus recommended. No significant differences in healing were found in comparisons between acyclovir and trifluridine. The comparison of ganciclovir to acyclovir is still limited by heterogeneity of available studies and possible publication bias. The joint use of two topical antivirals (RR 1.00; 95% CI 0.89 to 1.12) and the use of oral acyclovir alone (RR 0.92; 95% CI 0.79 to 1.07) or combined with a topical antiviral (RR 1.08; 95% CI 0.99 to 1.17) appeared as effective as single topical antiviral therapy. Compared to antiviral monotherapy, the combination of an antiviral with interferon (RR 1.03; 95% CI 0.99 to 1.07) or with debridement (RR 1.04; 95% CI 0.95 to 1.14) did not yield significantly better outcomes. The corneal epithelial healing outcome improved when antiviral therapy followed debridement (RR 1.21; 95% CI 1.04 to 1.42).\textsuperscript{18} Intrastromal injections of depot bethametasone and acyclovir aimed at prolonged delivery into the avascular corneal tissue have been used with success.\textsuperscript{20}

Herpetic Stromal Disease

The Herpetic Eye Disease Study was designed to evaluate oral acyclovir for herpetic stromal keratitis.\textsuperscript{21} Five randomized double masked placebo controlled multicentre trials studied specific therapeutic protocols as follow:

A. Controlled trial of oral acyclovir for herpes simplex keratitis: Designed to evaluate the efficacy of oral acyclovir in treating stromal keratitis in patients receiving concomitant topical steroids and trifluridine. One hundred four patients randomized to receive a 10–week course of oral acyclovir 400 mg five times daily or placebo. By 16 weeks approximately two thirds of patients on either group had failed treatment. This trial concluded that there was no clinically significant beneficial effect of oral acyclovir in treating HSV stromal keratitis in patients receiving topical steroids and antiviral.\textsuperscript{22}

B. Controlled trial of topical corticosteroids for herpes simplex stromal keratitis. This trial studied the efficacy of topical steroids in stromal keratitis. One hundred six patients with active stromal disease who had not received steroids were enrolled. Patients were randomized to placebo or steroid group (n=49 and 57 respectively). Regimens were tapered over the next 10 weeks. Both groups received topical trifluridine. Compared with placebo, patients on steroid treatment reduced the risk of persistent or progressive stromal kerato-uveitis by 68%. The treatment group had a significantly shorter time to resolution. It is important to note that delaying treatment (steroid) did not have a negative effect on the visual outcome at 6 months and the recurrence rate was not altered by the use of steroids. The conclusion from this trial is that topical steroid treatment was better than placebo in herpetic stromal keratitis.\textsuperscript{23}
### Treatment recommendation

<table>
<thead>
<tr>
<th>Disease</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Scleritis conjunctivae</td>
<td>- Oral acyclovir (400 mg 5 times a day for 7 days)</td>
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<tr>
<td>- Oral valacyclovir</td>
<td></td>
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<tr>
<td>500 mg 3 times a day</td>
<td></td>
</tr>
<tr>
<td>Epithelial disease</td>
<td>- Acyclovir 3% / ganciclovir 0.15% ointment 5 times a day until the ulcer heals continued with 3 times a day for 7 more days. Alternatively use trifluridine every 2 hours while awake until re-epithelialization followed by 5 times a day for one more week.</td>
</tr>
<tr>
<td>- Oral acyclovir or valacicylovir</td>
<td></td>
</tr>
<tr>
<td>Stromal disease</td>
<td>- Oral and topical antiviral treatment as above plus topical prednisolone acetate 1% every 2 hours while awake tapered as needed until inflammation resolves.</td>
</tr>
<tr>
<td>Iridocyclitis/endothelial disease</td>
<td>- Oral antiviral (as above) and topical steroids as needed to control inflammation.</td>
</tr>
</tbody>
</table>

C. Controlled clinical trial of oral acyclovir for iridocyclitis caused by herpes simplex virus: This study was performed to evaluate the use of oral acyclovir added to a regime of topical steroids and trifluridine in patients with HSV iridocyclitis. Patients were randomized to a 10-week course of acyclovir 400 mg 5 times daily or placebo while using topical steroids and trifluridine. The trial was stopped before conclusion because of difficulties related to recruitment; however, treatment failure occurred in 50% of the treatment group and in 68% of the placebo and the results suggested a possible benefit of oral acyclovir in the treatment of iridocyclitis. 24

D. Controlled clinical trial of oral acyclovir for the prevention of stromal keratitis or iritis in patients with HSV epithelial keratitis: Patients were randomized to receive a 3-week course of oral acyclovir 400 mg five times a day or placebo. The conclusion of this study revealed that there is no apparent benefit of oral acyclovir treatment added to topical trifluridine for the prevention of stromal disease or anterior uveitis. 25

E. Controlled clinical trial of oral acyclovir for prevention of recurrent HSV eye disease: 703 patients with history of HSV eye disease in the preceding 12 months were enrolled and randomized to 400 mgs of oral acyclovir or placebo. The probability of HSV during the 12-month period was 19% and 32% for the treatment and placebo groups respectively. The conclusion of this trial is that long term oral prophylaxis reduces the rate of recurrences especially in the subgroup of patients with previous history of stromal HSV. 25

The different conclusions for the HEDS study and the different systematic reviews available are good starting point for the planning of a therapeutic strategy for a given patient. Treatment should be designed on an individual perspective, based on the available evidence but taking into account the patients medical and ocular condition, previous therapeutic failures or successes, the severity of the disease and visual threat, the potential for visual rehabilitation and the socio-economic environment in which the patient lives.

Prophylaxis may also vary from patient to patient but we recommend oral antiviral treatment since long-term use of topical antivirals is toxic to the ocular surface. 11 Lifelong treatment may be necessary for patients with recurrent severe stromal disease, those with corneal transplantation for HSV disease or those with single eye. We recommend oral acyclovir 400 mgs twice daily or oral valacyclovir 500 mgs daily. The renal function has to be monitored. In the given scenario that a patient with HSV ocular disease may require ocular surgery of any type, prophylaxis is recommended starting at least 7 days before the procedure and continued for a reasonable time afterwards (1 to 18 months) depending on the severity of the previous episodes, visual function and surgery performed. 26

### REFERENCES