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Role of Intravenous Acyclovir in Treatment of Herpes Simplex Virus Stromal Keratitis with Ulceration: A Review of 2 Cases

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Data Collection B
Statistical Analysis C
Data Interpretation D
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Conflict of interest: None declared

Case series
Patients: Male, 78-year-old • Male, 27-year-old
Final Diagnosis: Herpes necrotizing keratitis
Symptoms: Visual acuity loss
Medication: —
Clinical Procedure: —
Specialty: Ophthalmology

Objective: Unusual clinical course

Background: Herpes simplex virus (HSV) stromal keratitis with ulceration is one of the most serious forms of herpes corneal infection and is one of the most difficult conditions in terms of clinical management. We assessed the efficacy of intravenous acyclovir in the treatment of this condition.

Case Reports: Two cases of HSV stromal keratitis with ulceration were reported in terms of clinical presentation, investigation, treatment, and outcome.Diagnosis was confirmed by polymerase chain reaction (PCR) analysis. PCR testing of corneal scraping samples identified HSV-1 in the first patient and HSV-2 in the second patient. The first patient initially presented with herpes geographic epithelial keratitis and progressed to HSV stromal keratitis with ulceration during treatment with a prophylactic dose of oral acyclovir. Despite oral acyclovir therapy, the cornea lesion continued to worsen. The treatment was switched to intravenous acyclovir. The stromal infiltration gradually improved, and the epithelial defect closed. The second patient, who had undergone penetrating keratoplasty for 13 years, presented with extensive corneal infiltration and corneal melting. The laboratory work-up was positive for HSV-2, and intravenous acyclovir was prescribed. The patient's corneal infiltration improved, but a persistent epithelial defect was present. Then, 100% autologous serum was used until the epithelial defect closed. Prophylactic treatment with oral acyclovir was prescribed to both patients to prevent disease recurrence.

Conclusions: Intravenous acyclovir might be considered as an alternative treatment for patients with HSV stromal keratitis with ulceration who do not respond to oral acyclovir or those with an extensive infection on a corneal graft.

Keywords: Acyclovir • Corneal Ulcer • Keratitis, Herpetic

Abbreviations: **AUC** – area under the ROC curve; **BCVA** – best-corrected visual acuity; **CMV** – cytomegalovirus; **EBV –** Epstein-Barr virus; **HSV** – herpes simplex virus; **HHV6** – human herpesvirus 6; **KPs** – keratic precipitates; **PCR** – polymerase chain reaction; **VZV** – varicella zoster virus

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Background

Herpes simplex virus (HSV) keratitis is a major infectious cause of corneal blindness, especially in developed countries [1]. HSV can affect all layers of the cornea, and it is associated with a wide range of clinical presentations. HSV stromal keratitis with ulceration, previously called HSV necrotizing stromal keratitis [2], is an uncommon manifestation of HSV stromal disease that is caused by either direct HSV invasion into the corneal stroma or severe local immune response [3].

HSV stromal keratitis with ulceration is considered one of the most serious forms of herpes corneal infection and one of the most difficult in terms of clinical management. Because HSV DNA has been detected in corneal tissue in patients with HSV necrotizing keratitis, antiviral drugs are mandatory to control viral replication, and they can be administered topically or systemically [4]. Moreover, steroids are also recommended as treatment options for this condition [5-7]. To date, there has been only 1 case report of using intravenous acyclovir in an immunocompromised patient with herpetic epithelial keratitis. In the report, the patient responded to intravenous acyclovir but not topical or oral acyclovir [8]. In the present report, we described 2 interesting cases of HSV stromal keratitis with ulceration that were successfully treated with intravenous acyclovir. One case occurred on a decompensated cornea, and the second occurred on a corneal graft. Ethics approval was obtained from the Ethics Committee of the institute (MURA2020/1134) before the patients' clinical data were reported.

Case Reports

Case No. 1

A 78-year-old man was diagnosed with pseudophakic bullous keratopathy from a previous phacoemulsification in his right eye. He presented with progressive pain, redness, tearing, photophobia, and decreased vision for 1 week in his right eye. He had no underlying disease. On initial clinical examination, the best-corrected visual acuity (BCVA) was light projection in the right eye and 20/70 in the left eye. Slit-lamp examination of the right eye revealed geographic epithelial keratitis (Figure 1A, 1B). Corneal scraping was performed as a standard

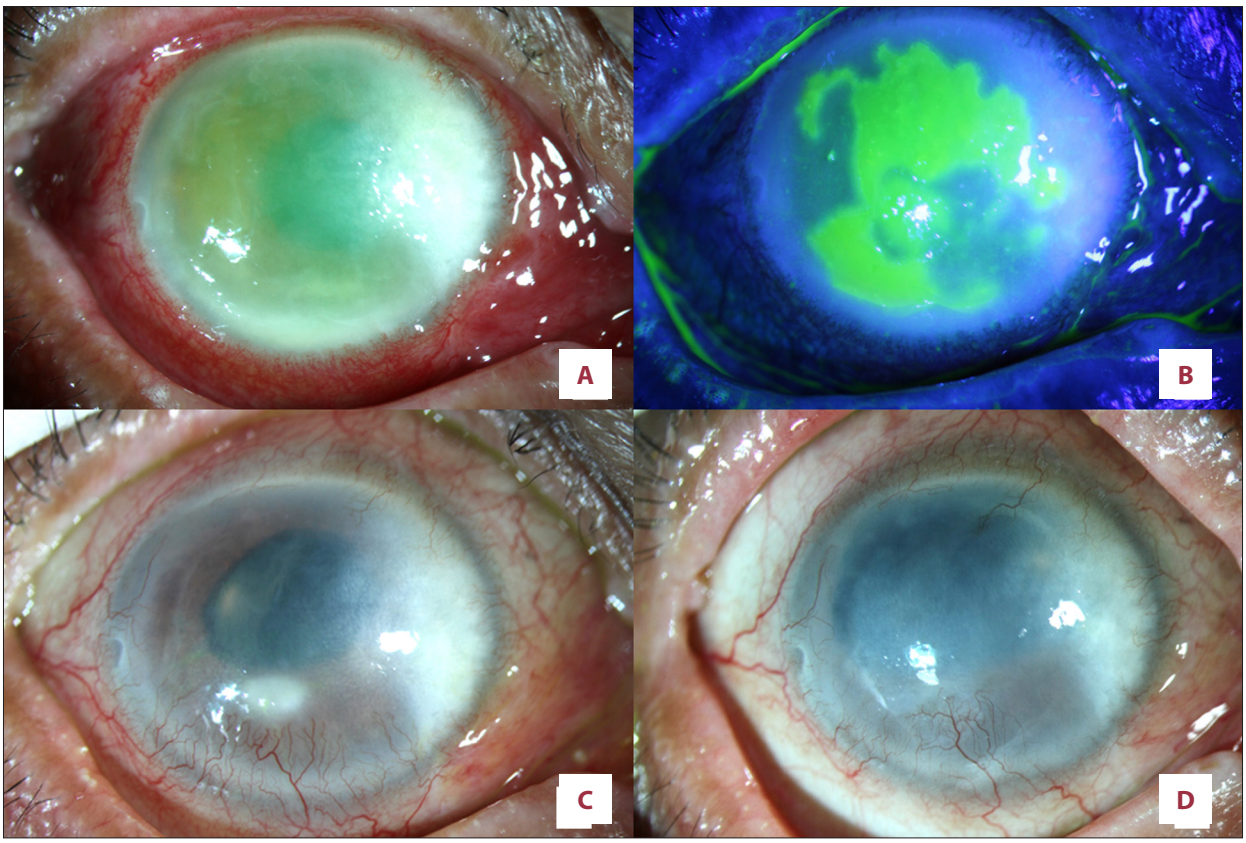

Figure 1. Slit-lamp photographs showing corneal lesion of patient No. 1 (**A, B**) At the first presentation, demonstrating classic clinical corneal lesion of geographic epithelial keratitis. (**C**) At 2 weeks after healing of epithelial keratitis, showing new paracentral anterior stromal infiltration with overlying epithelial defect. (**D**) After intravenous acyclovir treatment, resolution of corneal infiltration and healing of epithelial defect.

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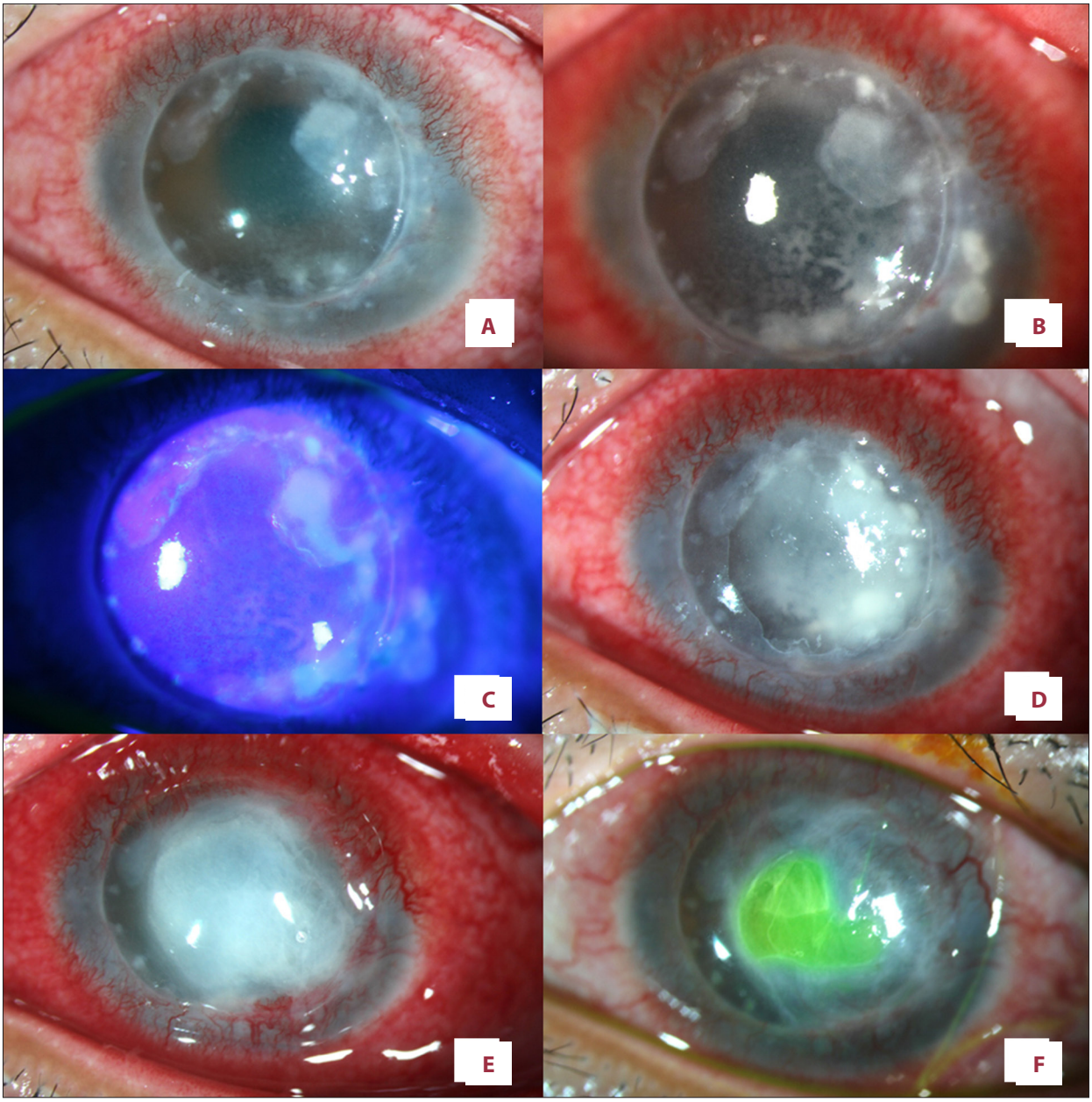

Figure 2. Slit-lamp photographs showing clinical progression of patient No. 2. (**A**) On day 1, eccentric, well-defined edge anterior one-third of stromal infiltration with overlying epithelial defect. (**B, C**) On day 3, progression of anterior stromal infiltration and scalloped-shaped border of epithelial defect demonstrated by fluorescein staining. (**D**) On day 7, multifocal, large, deep and dense anterior stromal infiltration with corneal melting. (**E**) On day 12 (after 3 days of intravenous acyclovir), improvement of stromal infiltration, but still of stromal melting at center of the lesion. (**F**) On day 30 (after 1 week of autologous serum eye drops), improvement of corneal melting and decreasing size of epithelial defect.

microbiological investigation. The diagnosis of HSV-1 epithelial keratitis was confirmed by polymerase chain reaction (PCR). After the administration of oral acyclovir 400 mg 5 times daily for 5 days, the epithelial defect was completely healed. When he completed a 14-day treatment course of acyclovir, prophylactic acyclovir at 400 mg twice daily was continued. However, 2 weeks after taking the prophylactic dose, he presented with redness and tearing in his right eye again. Slit-lamp examination revealed a paracentral 2×2 mm anterior stromal infiltration with an overlying epithelial defect (**Figure 1C**). Pigmented keratic precipitates (KPs) were observed, but there was no anterior chamber reaction. The intraocular pressure was 10 mmHg. HSV stromal keratitis with ulceration was suspected. We increased the frequency of acyclovir 400 mg to 5 times

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daily and prescribed 0.5% moxifloxacin eye drops 4 times daily. After 2 weeks of acyclovir treatment, no clinical improvement was observed. We performed corneal scraping for bacterial and fungal cultures and submitted the samples for PCR analysis for HSV, varicella zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), and human herpesvirus 6 (HHV6) DNA. After admission, the patient was treated with intravenous acyclovir (500 mg every 8 hours) plus topical 1.4% gentamicin and 5% cefazolin every hour until midnight to treat possible bacterial infections. On hospital day 3, PCR was positive for HSV-1, whereas the other cultures were negative. We continued intravenous acyclovir and decreased the frequency of topical antibiotics. Stromal infiltration and the epithelial defect were gradually improved. After 10 days of intravenous acyclovir, we switched to oral acyclovir 800 mg 5 times a day for 11 days and topical 0.5% moxifloxacin 6 times per day. We started 0.1% dexamethasone eye drops 2 times daily to reduce inflammation until the epithelial defect closed (**Figure 1D**). Because recurrent herpes keratitis occurred during treatment with the prophylactic dose of acyclovir 400 mg twice a day, we double the dose of acyclovir to 800 mg twice daily to prevent disease recurrence. No recurrence was observed during 4 months of follow-up. The patient's visual acuity was hand motion.

Case No. 2

A 27-year-old healthy man presented with pain and redness in his left eye for 1 week. He had undergone penetrating keratoplasty for a corneal scar at 14 years of age and continued treatment with fluorometholone eye drops once daily. He had a history of concurrent herpes epithelial and stromal keratitis on a graft 10 years ago. His vision decreased from 20/100 to counting fingers. Slit-lamp examination revealed eccentric, anterior stromal infiltration with an overlying epithelial defect (**Figure 2A**). There was a dense anterior chamber reaction with generalized fresh KPs. No hypopyon was noted. The rest of the ocular examination was unremarkable. Corneal scraping was performed. Confocal microscopy revealed no fungal hyphae or any obvious abnormalities. Because of acute-onset and suppurative stromal infiltration with distinct edges of the lesion, bacterial keratitis was suspected. We started treatment with topical 1.4% gentamicin and 5% cefazolin every hour until midnight; however, his corneal lesion became larger and progressed to posterior stroma. Fluorescein staining disclosed the scalloped-shaped border of the epithelial defect. The severity of anterior chamber inflammation and KPs was significantly increased (**Figure 2B, 2C**). The initial microbiological investigations were negative for bacteria and fungi. We switched the antibiotic to 5% vancomycin and 5% ceftazidime eye drops, but the stromal infiltration worsened. Therefore, 5% natamycin and 0.3% amphotericin eye drops were added. The stromal infiltrate progressively extended to 70% of the thickness of the corneal graft (**Figure 2D**). Corneal scraping was repeated, and the samples were sent for standard microbiological investigation and PCR analysis for HSV, VZV, CMV, EBV, and HHV6 DNA. The PCR result was positive for HSV-2, and herpes necrotizing stromal keratitis was diagnosed. Because of extensive stromal infiltration and corneal tissue melting, we started intravenous acyclovir (500 mg every 8 hours). Stromal infiltration and anterior chamber reaction were gradually improved (**Figure 2E**). Twice-daily topical 1% prednisolone acetate eye drops were added. After 8 days of intravenous acyclovir, we switched to oral acyclovir 400 mg 5 times a day for 13 days. Although the inflammation subsided, the epithelial defect persisted, leading to underneath stromal melting (**Figure 2F**). We stopped topical steroids and prescribed 100% autologous serum eye drops every hour in the daytime. Two weeks after starting autologous serum, the epithelial defect had closed. The final visual acuity was counting fingers. There has been no further recurrence in the 6 months of follow-up. We planned to prescribe the patient life-long oral acyclovir prophylaxis (800 mg per day).

Discussion

HSV stromal keratitis with ulceration is a rare manifestation of HSV infection that is believed to result from direct invasion of the corneal stroma [3]. However, some studies demonstrated that immunological responses by T cells, neutrophils, and macrophages also contributed to tissue damage [9,10]. The clinical features include dense infiltration and necrosis of the corneal stroma with an overlying epithelial defect. The diagnosis is generally rendered according to characteristic findings such as previous episodes of any type of herpes keratitis and typical features of HSV keratitis (eg, dendritic lesions, stromal edema with endothelial KPs localizing at the area of corneal involvement, and severe iritis), as well as the elimination of other causes of infection [6,7,11]. PCR is a rapid and reliable tool for definitively diagnosing HSV infection [12,13].

Currently, 3 topical (trifluridine, ganciclovir, and acyclovir) and 3 systemic (acyclovir, famciclovir, and valacyclovir) antiviral agents are available and actively used in the treatment of herpetic keratitis [14]. Topical trifluridine solution and acyclovir ointment and oral acyclovir and valacyclovir have been reported to achieve adequate corneal tissue therapeutic levels in human and animal models [15-17]. However, topical trifluridine and acyclovir were not commercially available in Thailand at the time of manuscript preparation; thus, the systemic formulations are always prescribed. Oral acyclovir was administered to the first patient. However, his clinical condition was not improved after 2 weeks. The poor response to oral acyclovir in our case possibly caused from a low dose of oral acyclovir (400 mg 5 times a day) and poor bioavailability of oral

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administration. This supported the treatment guideline for HSV keratitis from the American Academy of Ophthalmology (AAO), which recommends a high dose of acyclovir (800 mg 5 times a day) for HSV necrotizing keratitis [5]. However, it has been reported that some cases of HSV keratitis are resistant to acyclovir [18,19]. Interestingly, Duan et al found that the prevalence of acyclovir resistance among immunocompetent patients presenting with HSV keratitis was as high as 6.4% [20]. Mutation of thymidine kinase accounted for most cases of acyclovir resistance [20]. Another cause of poor response in our patient was the poor bioavailability of oral acyclovir. The use of intravenous acyclovir or its prodrug oral valacyclovir can result in improved bioavailability [21,22]. Human studies suggested that the bioavailability of intravenous acyclovir is comparable to that of oral valacyclovir in terms of the mean AUC, peak plasma concentration, and plasma elimination half-life [22,23]. For case No. 1, we first switched the treatment to intravenous acyclovir. After changing the treatment, the patient's corneal infiltration was significantly improved. This amelioration might have resulted from the improvement of drug bioavailability. It should be noted that a high dose of oral acyclovir (800 mg 5 times daily) or oral valacyclovir (1 g 3 times daily) could possibly result in similar outcomes compared to an intravenous form. Further clinical studies are needed to determine the best option for treatment of HSV stromal keratitis with ulceration.

We decided to start intravenous acyclovir at the beginning of treatment without providing the oral formulation in case No. 2 because he presented with severe keratitis on the corneal graft. Some studies demonstrated that intravenous acyclovir can rapidly achieve peak plasma concentrations after infusion compared with the findings for oral valacyclovir [22,24]. Dutt et al reported that patients with herpes necrotizing keratitis have worse clinical outcomes when the diagnosis is delayed [11]. The use of intravenous acyclovir therapy in patients with severe ocular HSV necrotizing stromal keratitis with ulceration might be an alternative option. However, the maintenance of hydration and monitoring of urine output should be considered to avoid renal toxicity during drug administration.

It has been established that severe local inflammatory responses can also damage the cornea in patients with necrotizing stromal keratitis [3]. Thus, titration of the dose of anti-inflammatory agents such as corticosteroids is needed. The AAO guideline for corticosteroid therapy recommends a low dose of topical 1% prednisolone twice daily in patients with necrotizing stromal keratitis [5]. We found delayed epithelial healing with stromal melting in case No. 2, then the topical steroid was stopped. Corneal wound healing should be closely monitored after prescribing a topical steroid in patients with stromal keratitis and ulceration. Delayed epithelial healing is a common problem after herpes stromal keratitis, which can also be associated with neurotrophic keratopathy [25]. Some studies described the effectiveness of 20% autologous serum in facilitating corneal epithelial healing in patients with herpes keratitis and neurotrophic keratopathy [26,27]. Our prior study demonstrated that 100% serum eye drops are also effective, safe, and well-tolerated in patients with persistent epithelial defects (25 of 109 eyes exhibited neurotrophic keratopathy) [28]. We successfully used 100% serum to facilitate the healing of the epithelial defect in patient No. 2. Diluted or undiluted serum eye drops could be considered as a less invasive alternative in the context of persistent epithelial defects after herpes keratitis before proceeding to amniotic membrane transplantation.

Conclusions

HSV necrotizing keratitis should be suspected early in patients with corneal ulcers who have a history of herpes simplex infection or who present with some characteristics of herpes infection such as geographic border or prominent KPs in the anterior chamber. Oral acyclovir can be prescribed earlier in the course because the benefits outweigh the low toxicity profile of the drug. Intravenous acyclovir 500 mg every 8 hours for 7-10 days might be considered as an alternative treatment for patients with HSV stromal keratitis with ulceration who do not respond to oral acyclovir or those with an extensive infection on a corneal graft.

Ethics Statement

The study protocol was approved by the Human Research Ethics Committee of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University (MURA2020/1134) and informed consent was obtained from the patients. This study strictly adhered to the principles of the Declaration of Helsinki.

Conflict of Interests

None.

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References:

1. Liesegang TJ. Epidemiology and natural history of ocular herpes simplex virus infection in Rochester, Minnesota, 1950-1982. Trans Am Ophthalmol Soc. 1988;86:688-724
2. Chodosh J, Ung L. Adoption of innovation in herpes simplex virus keratitis. Cornea. 2020;39(Suppl. 1):S7-S18
3. Kaye S, Choudhary A. Herpes simplex keratitis. Prog Retin Eye Res. 2006;25(4):355-80
4. Brik D, Dunkel E, Pavan-Langston D. Herpetic keratitis: Persistence of viral particles despite topical and systemic antiviral therapy. Report of two cases and review of the literature. Arch Ophthalmol. 1993;111(4):522-27
5. White ML, Chodosh J. Herpes simplex virus keratitis: a treatment guideline. Hoskins Center for Quality Eye Care and American Academy of Ophthalmology Website; 2014. *https://www.aao.org/clinical-statement/herpes-simplex-virus-keratitis treatment-guideline*
6. Heiligenhaus A, Li H, Hernandez Galindo EE, et al. Management of acute ulcerative and necrotizing herpes simplex and zoster keratitis with amniotic membrane transplantation. Br J Ophthalmol. 2003;87(10):1215-19
7. Shi W, Chen M, Xie L. Amniotic membrane transplantation combined with antiviral and steroid therapy for herpes necrotizing stromal keratitis. Ophthalmology 2007;114(8):1476-81
8. Oshry T, Lifshitz T. Intravenous acyclovir treatment for extensive herpetic keratitis in a liver transplant patient. Int Ophthalmol. 1997;21(5):265-68
9. Bauer D, Mrzyk S, van Rooijen N, et al. Macrophage-depletion influences the course of murine HSV-1 keratitis. Curr Eye Res. 2000;20(1):45-53
10. Jayaraman S, Heiligenhaus A, Rodriguez A, et al. Exacerbation of murine herpes simplex virus-mediated stromal keratitis by Th2 type T cells. J Immunol. 1993;151(10):5777-89
11. Dutt S, Acharya M, Gour A, et al. Clinical efficacy of oral and topical acyclovir in herpes simplex virus stromal necrotizing keratitis. Indian J Ophthalmol. 2016;64(4):292-95
12. Acharya M, Dave A, Farooqui JH. Commentary: Herpes keratitis: A diagnostic challenge. Indian J Ophthalmol. 2019;67(7):1046-47
13. Satpathy G, Mishra AK, Tandon R, et al. Evaluation of tear samples for herpes simplex virus 1 (HSV) detection in suspected cases of viral keratitis using PCR assay and conventional laboratory diagnostic tools. Br J Ophthalmol. 2011;95(3): 415-418.
14. Tsatsos M, MacGregor C, Athanasiadis I, et al. Herpes simplex virus keratitis: An update of the pathogenesis and current treatment with oral and topical antiviral agents – response. Clin Exp Ophthalmol. 2017;45(3):317
15. Pavan-Langston D, Nelson DJ. Intraocular penetration of trifluridine. Am J Ophthalmol. 1979;87(6):814-18
16. Poirier RH, Kingham JD, de Miranda P, et al. Intraocular antiviral penetration. Arch Ophthalmol. 1982;100(12):1964-67
17. Dias C, Nashed Y, Atluri H, et al. Ocular penetration of acyclovir and its peptide prodrugs valacyclovir and val-valacyclovir following systemic administration in rabbits: An evaluation using ocular microdialysis and LC-MS. Curr Eye Res. 2002;25(4):243-52
18. Toriyama K, Inoue T, Suzuki T, et al. Necrotizing keratitis caused by acyclovir-resistant herpes simplex virus. Case Rep Ophthalmol. 2014;5(3):325-28
19. Zhang W, Suzuki T, Shiraishi A, et al. Dendritic keratitis caused by an acyclovir-resistant herpes simplex virus with frameshift mutation. Cornea. 2007;26(1):105-6
20. Duan R, de Vries RD, Osterhaus AD, et al. Acyclovir-resistant corneal HSV-1 isolates from patients with herpetic keratitis. J Infect Dis. 2008;198(5):659-63
21. de Miranda P, Blum MR. Pharmacokinetics of acyclovir after intravenous and oral administration. J Antimicrob Chemother. 1983;12(Suppl. B):29-37
22. Höglund M, Ljungman P, Weller S. Comparable aciclovir exposures produced by oral valaciclovir and intravenous acyclovir in immunocompromised cancer patients. J Antimicrob Chemother. 2001;47(6):855-61
23. Soul-Lawton J, Seaber E, On N, et al. Absolute bioavailability and metabolic disposition of valaciclovir, the L-valyl ester of acyclovir, following oral administration to humans. Antimicrob Agents Chemother. 1995;39(12):2759-64
24. de Miranda P, Whitley RJ, Blum MR, et al. Acyclovir kinetics after intravenous infusion. Clin Pharmacol Ther. 1979;26(6):718-28
25. Hamrah P, Cruzat A, Dastjerdi MH, et al. Corneal sensation and subbasal nerve alterations in patients with herpes simplex keratitis: An in vivo confocal microscopy study. Ophthalmology. 2710;117(10):1930-36
26. Matsumoto Y, Dogru M, Goto E, et al. Autologous serum application in the treatment of neurotrophic keratopathy. Ophthalmology. 2004;111(6):1115-20
27. Guadilla AM, Balado P, Baeza A, et al. [Effectiveness of topical autologous serum treatment in neurotrophic keratopathy]. Arch Soc Esp Oftalmol. 2013;88(8):302-6 [in Spanish]
28. Lekhanont K, Jongkhajornpong P, Anothaisintawee T, et al. Undiluted serum eye drops for the treatment of persistent corneal epitheilal defects. Sci Rep. 2016;6:38143

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