Ganciclovir in the Treatment of Ophthalmic Viral Infections – Case Reports

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Abstract

Adenovirus is likely the most common cause of eye infections but remains a challenge for ophthalmologists to diagnose as well as treat. While ganciclovir gel is approved for the topical treatment of eye infections arising due to herpes simplex virus, it is not licensed for use against adenoviral conjunctivitis. This antiviral agent selectively targets infected cells and disrupts viral DNA replication. A small study and previous anecdotal reports had illustrated the potential of ganciclovir in improving symptoms and transmissibility of adenoviral eye infections. The present article describes a series of case studies where ganciclovir was used off label in the management of the morbidity caused by adenovirus. The observations are promising and suggest that ganciclovir can be used successfully in this patient population. However, large-scale randomised trials are needed to confirm these findings.

Keywords

Ganciclovir gel, adenoviral conjunctivitis, herpes simplex virus, off-label use, trifluridine toxicity, case studies

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Eye infections are common and represent a major healthcare burden. Herpes simplex virus type 1 (HSV-1) and, less commonly, HSV type 2 (HSV-2) have been responsible for ocular infections in approximately 400,000 Americans. Moreover, nearly 50,000 new and recurring cases are diagnosed annually in the US with a quarter of cases being the more serious stromal keratitis.[1] HSV is involved in the pathogenesis of several ocular disorders and may lead to numerous diseases including blepharitis, vesicular dermatitis of the eyelids, conjunctivits, keratitis, trabeculitis, anterior uveitis, acute retinal necrosis syndrome, retinitis and optic neuritis.[2] Adenovirus, however, is the most likely cause of the majority of eye infections.

Adenoviral conjunctivitis is the most frequent cause of red eye and can lead to significant morbidity in patients. Although very common, it remains a challenge for ophthalmologists to both diagnose and treat, mainly because of its non-specific presentation and the numerous conditions that can cause pink eye. Aside from the difficulties in diagnosis and treatment of patients, contagiousness and easy transmission to family members is part of the challenge. At present, clinicians generally only offer supportive measures to treat these patients.

Ganciclovir is an antiviral agent that is selectively active against viral DNA. This prodrug is a synthetic nucleoside analog of 2′-deoxyguanosine 9-(1,3-dihydroxy-2-propoxymethyl) guanine that is phosphorylated by the virus-encoded thymidine kinase.[2] Ganciclovir triphosphate then competitively inhibits incorporation of the endogenous nucleotide by the viral DNA polymerase. This results in replication arrest and damage to infected cells. Ganciclovir is currently approved by the US Food and Drug Administration to be used systemically and intravitreally against cytomegalovirus retinitis and, following positive results from clinical trials, topically (Ganciclovir ophthalmic gel; Zirgan®) against herpes simplex dendritic keratitis.[3] Topical application of ganciclovir has been shown to penetrate the corneal stroma and reach the aqueous humor at therapeutic levels.[4]

In May 2011, Yabiku and colleagues reported results of a double-blind, randomized clinical trial of 33 patients diagnosed with adenoviral conjunctivitis.[5] They compared the efficacy of ganciclovir ophthalmic gel against placebo in reducing and improving signs, symptoms and transmissibility. They found a trend to faster improvement and less transmissibility to the other eye and people living with affected patients in the treatment group, however these data were not statistically significant.

Table 1: Summary of patient details from the case reports

Patient	Age/Sex	Involved Eye	Conjunctival Signs	Injection Corneal Signs	Culture Signs	Time to Resolve Symptoms	Signs Resolved	Time to Resolved	Fellow Eye/ Others Affected	SEI at Last Visit
1	57/F	OD	Injection herpetic ulcer	Herpetic dendrite	Not done	94 days	Dendritiform epitheliopathy	94 days	No/No	None
2	58/F	OS	Injection + pseudomembranes	Epithelial erosion (80 %)	Not done	8 days	Erosion	8 days	Yes/No	Few residual
3	26/F	OS	Follicles injection	SPKs + staining SEIs	negative	10 days	Follicles injection SPKs staining	14 days	No/No	Few residual
4	45/M	OS	Follicles injection	None	negative	5 days	Follicles injection	7 days	No/No	None
5	59/M	OU	Follicles injection	SEI	Positive for adenovirus	14 days	Follicles injection	18 days	NA/No	Few residual

NA = not available; SPKs = superficial punctate keratitis; SEI = subepithelial infiltrate.

Despite the encouraging data thus far, ganciclovir is still not licensed for use against adenoviral infections of the eye.[6] Here, we report on four cases of the off-label use of ganciclovir ophthalmic gel in patients diagnosed with adenoviral conjunctivitis. An additional case detailing the use of other available treatments for ocular infections is also presented.

Case Reports

A description summary of the following case studies is provided in *Table 1*.

Case 1

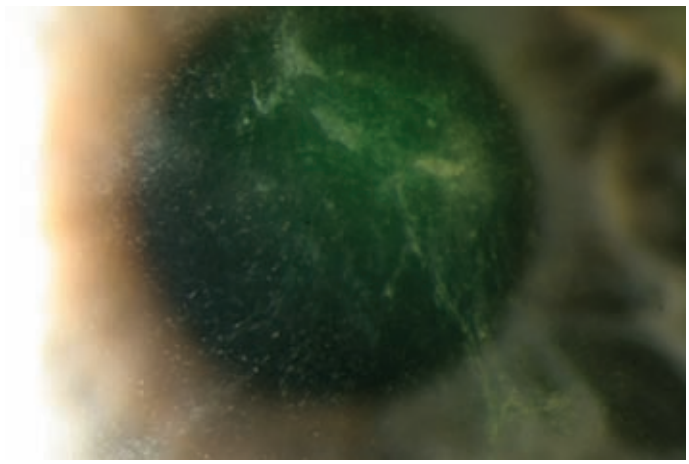
A 57-year-old caucasian female nurse presented to her ophthalmologist with a seven–day history of decreased vision associated with mild pain and redness OD. Her past ocular history was significant for two previous episodes of herpes simplex keratitis OD occurring 2–3 decades prior, 10–15 years of soft contact lens wear and amblyopia OS. Her past medical history was non-contributory and specifically negative for heart disease, hypertension, diabetes, stroke, thyroid dysfunction or a history of smoking.

On initial examination, her corrected vision was 20/30 OD and 20/100 OS. Slit lamp exam revealed a linear dendritic ulcer bisecting the visual axis OD. Given the patient's monocular status, she was treated aggressively with trifluridine (Viroptic®) four times daily (QID), acyclovir (Zovirax®) 400mg 5x daily, and gatifloxacin (Zymaxid®) QID. The dendrite healed within just three days, at which time prednisolone (Pred-Forte®) two times daily (BID) was added. A residual dendritiform epitheliopathy was noted, however, at the site of the original ulcer, prompting an increase of prednisolone to three times daily (TID). The epitheliopathy persisted, her vision declined in association with increased photophobia and on day 11 she was referred to our cornea service.

On presentation to us, her corrected vision was 20/200 OU. Slit lamp exam of the conjunctiva OD demonstrated diffuse injection and fluorescein staining revealed a gravitationally distributed 3/4+ inferior punctuate keratopathy. Her central cornea showed a similar field of 3/4+ staining keratopathy. Imbedded within this field was a distinct, vertically oblique, visual axis obscuring dendritiform lesion (see *Figure 1*). In the temporal mid-peripheral stroma were two inactive nummular opacities. There was no evidence of radial keratoneuritis.

Central corneal sensation by Cochet Bonnet aesthesiometry was 1.0 mm OD and 25–30 mm OS (normal ~45+mm). Schirmers with anesthesia were

Figure 1: Image of a Patient's Eye Showing a Distinct, Vertically Oblique, Visual Axis Obscuring Dendritiform Keratopathy Likely Related to Trifluridine Toxicity



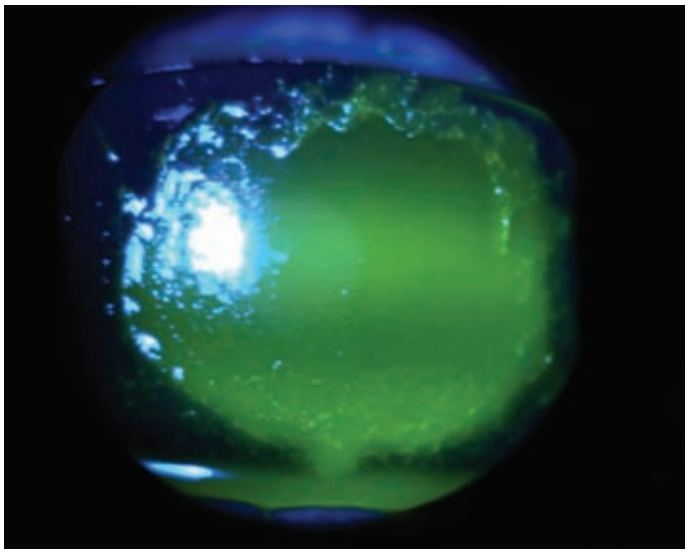
6.0 mm OD and 3.0 mm OS. Pain levels were reported as mild, never exceeding 2/10 from infection onset.

A multifactorial diagnosis was established including trifluridine toxicity OD, neurotrophic keratitis OD, active immune stromal keratitis OD, inactive infectious herpes simplex keratitis OD, aqueous deficient dry eye OU, corneal hypoesthesia OS and amblyopia OS. The trifluridine was discontinued and prednisolone reduced to BID.

At six days post trifluridine discontinuation, the corneal findings remained unchanged prompting silicone punctual plug insertion at the right lower lid, followed by a collagen plug at the right upper lid on day 10. Three days later, the diffuse keratopathy field had resolved, but the central dentritiform lesion remained. By post trifluridine day 19, the dendritiform lesion had had noticeably receded and the vision had improved to 20/80.

Throughout all of her visits to this point, the patient had expressed a highly emotional, frequently tearful, fear of blindness. On post trifluridine day 31, she was hospitalized secondary to a massive cerebrovascular accident (CVA) with associated hemi-paresis and dysphasia. She was not seen in our clinic again until post trifluridine

Figure 2. The Left Eye of a Patient Showing a Large Ragged-edged Epithelial Erosion Over 80 % of the Total Corneal Surface



day forty-two. At that time she was wheelchair-bound, verbal only to yes/no responses, showed persistence of the dendritiform keratopathy but with the addition of exposure secondary to reduced blink rate and reduced corrected vision to 20/250. Her treatment regimen was adjusted to acyclovir 400mg BID, loteprednol (Lotemax®) BID, and non-preserved artificial tears as well as Refresh PM® QID. By post trifluridine day 59, her vision had improved to 20/40 and final keratopathy resolution with 20/20 vision was reached at day ninety-four.

Case 2

A 58-year-old caucasian female presented to her primary eye care provider complaining of a seven-day history of increasing lid swelling, redness, tearing, and foreign body sensation OS. Her past ocular history was significant only for LASIK OU performed seven years prior.

Uncorrected visual acuity was 20/20 OD and 20/40 OS. Slit lamp exam OD was unremarkable except for a lamellar LASIK scar. External and slit lamp exam OS was remarkable for left facial and periorbital edema, 2+ diffuse corneal superficial punctate keratitis (SPK) and a small focal 'dendritic' appearing epithelial defect. A diagnosis of left herpes zoster ophthalmicus was made and the patient was started on loteprednol TID, oral acyclovir and oral cephalexin (Keflex®). Unfortunately her condition deteriorated significantly overnight, and she presented the next day as an emergency to our cornea service.

At that time she complained of a further increase in lid swelling, pain, and loss of vision OS (20/250). In addition, she noted the onset of redness and irritation OD. Slit lamp exam OD revealed 3+ conjunctival injection but no acute corneal findings. The left eye now demonstrated 4+ haemorrhagic conjunctival injection and a large ragged-edged epithelial erosion comprising 80 % of the total corneal surface (see *Figure 2*). Severe epidemic adenoviral keratoconjunctivitis (EKC) was diagnosed, all previous ocular medications discontinued, and a new pharmacologic regimen instituted consisting of topical ganciclovir 5x daily OU, besifloxacin (Besivance®) BID OU, and nepafenac (Nevanac®) QID OU as needed for pain.

Follow-up two days later revealed essentially unchanged slit lamp findings OU, but improved comfort and vision OS (20/80). Examination four days post ganciclovir initiation revealed decreased injection OD and ~50 % closure of the epithelial defect OS. Complete closure was noted by day eight, with progressive clinical improvement OU thereafter. Subepithelial infiltrates (SEIs) appeared OS on treatment day 20, which progressed to a requirement for topical steroids (loteprednol) by day twenty-seven. Ganciclovir was discontinued OU on day twenty-seven.

A single SEI appeared OD on day 34, and persisted unchanged through to the last examination 11 months post infection. The left eye required continuous topical steroid treatment throughout the entire 11-month follow-up period. During the early infectious period, the patient was held off work for three full weeks.

Case 3

A 26-year-old female presented with a two-week history of redness, tearing and light sensitivity of the left eye. She also noticed enlargement of her left periauricular lymph node. She was diagnosed and treated for HSV conjunctivitis by another clinician with oral acyclovir and topical antibacterials, both of which she used with no relief of symptoms. Her past ocular history was significant for keratoconus in both eyes, for which she wore piggy-back lenses for best vision. Examination of the right eye revealed a best-corrected visual acuity of 20/30; she was wearing her piggy-back lenses on that eye. The rest of the anterior segment examination was unremarkable. Examination of the left eye revealed an uncorrected visual acuity of 20/400. She had follicular changes in the upper and lower palpebral conjunctivae, +2 conjunctival injection, and several coarse subepithelial corneal infiltrates. She had watery discharge and severe light sensitivity. She also had a prominent preauricular lymph node on the left. Fundus examination and tonometry were deferred in both eyes during that visit. Cultures from the left eye were sent for analysis. However, as the clinical findings were consistent with unilateral EKC, we decided to treat the patient for adenoviral infection. After discussing its off-label use, she was given ganciclovir ophthalmic gel, to be used 5x daily on the left eye for two days. She was also started on topical non-steroidal anti-inflammatory drugs (NSAIDs) and oral valacyclovir (Valtrex®). Two days later the viral cultures showed no growth. The patient was instructed to discontinue valacyclovir and to add loteprednol eye drops TID. She came back after two weeks with improvement of signs and symptoms. There were few residual asymptomatic SEIs. She was advised to discontinue ganciclovir gel and taper loteprednol over the next three weeks.

Case 4

A 45-year-old male presented with a one-day history redness, pain, and light sensitivity of the left eye. His past ocular history was significant for keratoconus in both eyes. He was status post penetrating keratoplasty in 1994 on the left eye, and wore rigid gas permeable (RGP) lenses in both eyes for best vision. He was being maintained on steroid drops once a day and cyclosporine drops BID on the left eye. Examination of the right eye revealed a best-corrected visual acuity of 20/20. Anterior

segment examination was unremarkable except for keratoconus with a well-fitted RGP lens. Examination of the left eye showed an uncorrected visual acuity of 20/400, mild lid edema, moderate conjunctival injection, and follicular changes on the upper and lower palpebral conjunctiva. His corneal graft was clear with no signs of graft rejection. These findings seemed to be consistent with unilateral acute viral conjunctivitis. Cultures were taken and sent for analysis. The patient expressed his concern regarding contagiousness to his children. After explaining its off-label use, he was started on ganciclovir gel 5x daily on the left eye. He was asked to continue use of steroid drops once a day. The cultures were negative for viral growth. He followed up after one week with much-improved signs and symptoms.

Case 5

A 59-year-old male presented with a one-day history of eye pain and redness in both eyes. This was associated with watery eye discharge, swelling, and slightly blurred vision. Examination of the both eyes showed visual acuities of 20/30, with conjunctival injection and follicular changes on the upper and lower palpebral conjunctivae. He had several subepithelial coarse infiltrates in both corneas. Swabs from both eyes were sent for viral culture. The clinical findings were suggestive of bilateral EKC and he was prescribed ganciclovir to be used 5x daily in both eyes. He was followed up after four days. Patient reported slight improvement of symptoms. There was no change in both conjuctival and corneal signs. Cultures were positive for adenovirus. The patient was asked to continue using ganciclovir gel and add steroid eye drops. On his next visit a week later, the patient reported complete resolution of his symptoms. Although conjunctival injection and follicles were still present, they resolved a week later. He had some residual SEIs, which were not affecting the visual axis. The patient refused to use steroids and was maintained on artificial tear drops.

Discussion

The first case of the series is a complex and ultimately tragic one that offers a poignant reminder of the risks of trifluridine toxicity, the extended timeframe potentially required for its reversal, and the unpredictable morbidities associated with that process. The pre-existing aqueous deficient dry eye, neurotrophic disease and post infectious inflammation, coupled with exposure to multiple preservative-containing medications including the highly toxic thimerosal-containing trifluridine predisposed this patient to severe and extended ocular surface disturbance. It is not difficult to invoke the stress of this preservative-related complication as an important etiologic element to this patient's otherwise non-predisposed massive and tragic CVA.

Although adenoviral EKC can clinically manifest in a highly asymmetric fashion and the latter four patients represent only a few anecdotal cases, they nevertheless raise intriguing possibilities regarding the potential application of ganciclovir for the treatment of at least some serotypes of adenoviral conjunctivitis.

In particular for Case 2, not only did ganciclovir appear to benefit this patient, but it seemed to clinically 'freeze' disease progression at the point of application. The left eye, one full week into symptomatic infection and demonstrating a highly virulent viral strain, began improving just two days after ganciclovir introduction. The right eye, treated just 24 hours into symptom manifestation, never progressed beyond moderate conjunctival injection.

Finally, the three weeks of lost working time suffered by this patient, not to mention the infection's possible spread to family, friends and co-workers, highlight the potential magnitude of personal, professional and economic morbidity associated with adenoviral conjunctivitis. It also emphasizes the value of an effective therapeutic intervention which to this point has not been available.

Eye infection, i.e. conjunctivitis, is the most common diagnosis in a general ophthalmologist's clinic and it is most often caused by adenovirus. There are numerous serotypes—serotypes 1–11 and 19 cause follicular conjunctivitis, serotypes 3, 4, 5 and 7 cause pharyngoconjunctival fever, serotypes 3, 4, 8, 11, 19 and 37 acute conjunctivitis, and serotypes 8, 9 and 37 cause epidemic keratoconjunctivitis.[7] Since all the serotypes may have similar clinical presentations, it becomes a challenge to both diagnose and treat adenoviral conjunctivitis. Initial diagnosis of this condition can be erroneous and it can be confused with bacterial or herpetic keratoconjunctivits. Previously used diagnostic techniques such as viral culture, direct fluorescence antibody staining, polymerase chain reaction, and enzyme-linked immunosorbent assay, were limited due to longer time needed to achieve results, lower sensitivity or cost of the equipment. As seen in the above cases, even cultures are often negative for any growth. Early and accurate diagnosis is crucial in the management of adenoviral conjuctivitis, enabling physicians to take precautionary measures to limit transmission of infection, development of SEIs and other serious complications such as pseudomembrane formation. A new in-office, rapid, easy-to-use assay, the RPS Adeno Detector (Rapid Pathogen Screening Inc., Sarasota, Florida, US), is now available to make a specific and sensitive diagnosis of adenoviral infection.[8] Early and accurate diagnosis of this condition can justify isolating patients or advising them to take sanitary precautions, to initiate appropriate treatment and to prevent unnecessary antibiotic use.

Currently, there is no approved treatment for adenoviral conjunctivitis and management is usually symptomatic and supportive.[9] Recently, antivirals such as cidofovir (Vistide®) have been shown to be effective against some adenoviral serotypes; however, clinical use has been limited due to their toxicities.[10,11] Ganciclovir is clinically effective and approved against herpesvirus infections when applied topically onto the eye.[12] Its mechanism of action involves inhibiting viral DNA replication through direct incorporation into viral DNA following its phosphorylation by viral thymidine kinase. This results in eventual termination of viral DNA elongation.[12,13] It also makes the drug specific for infected cells and thus less toxic to non-affected cells.

In 1997, Chen and colleagues gave the first report on the use of systemic ganciclovir against adenovirus.[14] They described a case of a 47-year-old patient who was successfully treated for culture positive adenoviral hemorrhagic cystitis using systemic ganciclovir. Since then, several *in vitro* and *in vivo* studies have suggested that ganciclovir can control and treat adenoviral infections.[15–17]

In adenoviral keratoconjunctivitis, it has been suggested that ganciclovir can help achieve faster resolution of signs and symptoms,[5,18] reduce contagiousness of the disease[5] and prevent subepithelial opacities.[18] In our experience with the presented cases, ganciclovir appeared to have lessened the degree of symptoms and signs. Interestingly, none of the latter three patients reported transmission of infection to their close contacts. One patient had no SEIs and the other two had very few residual SEIs on their last visit. None of them had any serious complications such as pseudomembrane formation or decrease in vision. While it is difficult to draw firm conclusions from these observations, our experience here suggests that ganciclovir may prevent transmissibility as well as very severe ramifications of adenoviral keratoconjunctivitis. Current evidence remains limited and the role of ganciclovir in the prophylaxis and treatment of adenoviral keratoconjunctivitis needs to be explored further.

Summary and Conclusion

Ganciclovir as a topical gel has been successful in the treatment of ocular infections resulting from HSV. However, evidence supporting the application of this agent in preventing and treating adenovirus-based infections is lacking. There are currently no large-scale studies comparing the efficacy of ganciclovir with other therapeutic options in resolving adenoviral keratoconjunctivits. In this article, a series of cases was presented that illustrate the potential role ganciclovir can have in treating this disease. In all patients, ganciclovir improved symptoms of adenoviral infections with minimal toxicity and adverse effects. These observations may support the off-label use of ganciclovir in this patient population. However, well-designed, randomized trials are needed to provide definitive conclusions regarding this indication. ■

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