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REVIEW

Management of Adenoviral Keratoconjunctivitis: Challenges and Solutions

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Abstract: Human adenovirus (HAdV) is the most common cause of infectious conjunctivitis, accounting for up to 75% of all conjunctivitis cases and affecting people of all ages and demographics. In addition to ocular complications, it can cause systemic infections in the form of gastroenteritis, respiratory disease, and dissemination in immunocompromised individuals. HAdV causes lytic infection of the mucoepithelial cells of the conjunctiva and cornea, as well as latent infection of lymphoid and adenoid cells. Epidemic keratoconjunctivitis (EKC) is the most severe ocular manifestation of HAdV infection, in which the presence of subepithelial infiltrates (SEIs) in the cornea is a hallmark feature of corneal involvement. SEIs have the tendency to recur and may lead to long-term visual disability. HAdV persistence and dissemination are linked to sporadic outbreaks of adenoviral keratoconjunctivitis. There is no FDA-approved antiviral for treating adenoviral keratoconjunctivitis, and as such, solutions should be proffered to handle the challenges associated with viral persistence and dissemination. Several treatment modalities have been investigated, both systemically and locally, to not only mitigate symptoms but reduce the course of the infection and prevent the risk of long-term complications. These options include systemic and topical antivirals, in-office povidone-iodine irrigation (PVI), immunoglobulin-based therapy, anti-inflammatory therapy, and immunotherapy. More recently, combination PVI/dexamethasone ophthalmic formulations have shown favorable outcomes and were well tolerated in clinical trials for the treatment of EKC. Possible, future treatment considerations include sialic acid analogs, cold atmospheric plasma, N-chlorotaurine, and benzalkonium chloride. Continued investigation and evaluation of treatment are warranted to reduce the economic burden and potential long-term visual debilitation in affected patients. This review will focus on how persistence and dissemination of HAdV pose a significant challenge to the management of adenoviral keratoconjunctivitis. Furthermore, current and future trends in prophylactic and therapeutic modalities for adenoviral keratoconjunctivitis will be discussed.

Keywords: human adenovirus, adenoviral keratoconjunctivitis, antivirals, immunotherapy, povidone-iodine, viral dissemination

Introduction

Human adenovirus (HAdV) is the most common cause of infection to the ocular surface, accounting for up to 75% of conjunctivitis cases.[1] The most common presentation is pharyngoconjunctival fever (PCF), which often occurs in children and manifests clinically with fever, pharyngitis, rhinitis, follicular conjunctivitis, and regional lymphoid hyperplasia.[2] Epidemic keratoconjunctivitis (EKC) is the most severe ocular form and is distinguished by its ability to invade the corneal epithelium, ranging in presentation from a keratitis to persistent and recurrent subepithelial infiltrates (SEIs). HAdV is highly contagious due to its unique

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structure and ability to evade the normal host's immune system. It is distinguished from other types of conjunctivitis in that it often involves the cornea, with potentially devastating visual complications. These features contribute to a heavy economic burden and necessitate the establishment of a standard treatment protocol.[1] In addition to the potential ocular manifestations of this virus, HAdV infections have the propensity to manifest systemically, in cases such as respiratory, urinary, and gastrointestinal tract (GIT) infections. This variety of presentations can infect a normal, healthy host, and also have an increased risk in immunocompromised individuals. Despite the detrimental effect that HAdV infections pose, there has yet to be an FDA-approved drug to treat these conditions, making management difficult. Even following the active phase of the disease, viral persistence and reactivation may occur. Oral and topical antivirals have been considered as off-label management solutions, but problems with efficacy, bioavailability, and therapeutic profiles have limited their use. With regards to EKC, topical disinfection during active cases as well as treatment of corneal sequelae using corticosteroids and immunosuppressive agents show promise. This review will focus on how persistence and dissemination of HAdV poses a significant challenge to the management of adenoviral keratoconjunctivitis. Furthermore, current and future trends in prophylactic and therapeutic modalities for adenoviral keratoconjunctivitis will be discussed.

Virology

HAdV belongs to the genus Mastadenovirus and family Adenoviridae. It is a nonenveloped virus with a linear dsDNA genome and icosahedral capsids. HAdV consists of 7 groups classified through genomic sequence analysis.[3] Adenoviral-based ocular surface infections are attributed to several subtypes of Group B and D HAdV. Generally, these viruses bind CD46, a ubiquitously expressed transmembrane protein, to infect the host.[4,5] Exposure of the host to HAdV is made possible through the interaction between adenoviral fiber protein and primary host cellular receptors such as CD46, sialic acid, and heparin-sulfate proteoglycan, all of which promote the attachment and internalization of HAdV.[6,7] Interactions between the penton base of the virus and vitronectin-binding integrins of the host support internalization and acidification of the endosome, triggering conformational changes to the viral capsid. This process culminates in the release of viral DNA genome into the host nucleus, where viral replication occurs.[2,7-9]

Challenges

HAdV causes a lytic infection of the mucoepithelial cells of the conjunctiva and cornea as well as a latent infection of lymphoid and adenoid cells.[10] Members of Groups B and D HAdV cause both GIT and ocular infections. See Table 1 for the subtypes of Group B and D HAdV.[11,12] HAdV type 3, 7, and 21 of Group B can cause keratoconjunctivitis, urinary tract infection, respiratory infection, and GIT infection. Group D HAdV can also cause both ocular and GIT infection. Some group B HAdV subtypes infect the respiratory tract. Group B HAdV including type 3, 7, 14, and 21 have been associated with acute respiratory distress (ARD) outbreaks.[2,12] HAdV types that cause ARD are transmitted through aerosolized droplets. It is important to note that both respiratory droplets and the fecal-oral transmission route from individuals with acute adenoviral infection, or even post-infection adenoviral shedding, play an important role in the transmission dynamics of HAdV infections.[2,13]

Persistent HAdV secretions in the tears may also occur even years following the resolution of acute ocular infection. T cells in tonsillar and adenoid lymphoid tissue serve as reservoirs for harboring HAdV, making it possible to develop latent adenoviral infections.[3,13,14] Reactivation of persistent latent adenovirus in the host is likely facilitated through the blockade of types I and II interferon (IFN) response that is required to inhibit expression of the HAdV E1A gene.[3]

Immunosuppressive steroid therapy can suppress the production of cytokines including TNF-alpha, type I IFN, and type II IFN, as well as depleted T cells and NK cells.[3,15,16] This inadvertently reduces the secretion of antiviral cytokines that play a major role in inhibiting viral replication. Inhibition of the

Table 1 Overview of Subtypes of Group B and D HAdV with Sites of Infection

Group	HAdV Subtypes	Site of Infection
Group B HAdV	3, 7, 11, 14, 16, 21, 34, 35, 50, 55, 66, 68, and 76–79	Conjunctiva, urinary tract, respiratory tract, and gastrointestinal tract
Group D HAdV	8, 9, 10, 13, 15, 17, 19, 20, 22–30, 32, 33, 36–39, 42–47, 51, 53, 54, 56, 58–60, 63–65, 67, 69–75, 80–88, and 90–103	Cornea, urinary tract, respiratory tract, gastrointestinal tract, and conjunctiva

Note: Data from these publications.[11,12]

IFN response allows for expression of the HAdV E1A gene, which results in reactivation and replication of HAdV DNA in epithelial cell associated with latently infected lymphoid tissue and consequential dissemination of HAdV.[3] Thus, immunosuppression could facilitate dissemination of adenovirus into the community since subclinical adenoviral infection of tonsillar and adenoid lymphoid tissue serve as a source of transmitting adenoviruses, particularly in immunocompromised children with no prior exposure and immunity to a particular strain of adenovirus.[17] Additionally, asymptomatic passage of adenovirus in the stool of patients with previous adenoviral GIT infection can also occur.[3,11]

Kosulin et al suggested that latent HAdV infection of the gut lymphoid cell could serve as a source of release of HAdV particles in the community.[18] Garnett et al demonstrated the asymptomatic persistence of group C adenovirus in human mucosal T lymphocytes or lymphoid tissue following primary adenoviral infection.[17] The stimulation of these adenovirus containing mucosal T-lymphocytes results in reactivation of latent HAdV with consequential leakage of reactivated viruses into intestinal epithelial cells, where adenoviruses undergo replication and subsequent shedding in stool.[11,17,19-21] This is indicative of persistent subclinical HAdV infection of the gut-associated lymphoid tissue.[20]

Immunocompetent individuals are likely to shed less HAdV into their stool, in contrast to those who are immunocompromised, where significant amounts of HAdV are released. Immunocompromised individuals are also more likely to have reactivation of HAdV with productive infection of intestinal epithelial cells and consequential extensive viral dissemination in the community. As such, in the immunocompromised state, reactivation of persistent latent HAdV is an essential cause of HAdV dissemination.[18] These resultant, latent adenoviral infections are considered a significant challenge in managing and containing the virus within the community due to persistent adenoviral shedding and its high propensity of spread via hand-to-eye contact by those contaminated with fecal matter.[18]

Another significant challenge in managing adenoviral infections, particularly in Group D HAdV, is the propensity for this group to cause oculogenital infection. Several published cases have demonstrated that Group D HAdV can be associated with concurrent urethritis and conjunctivitis.[22–26] HAdV 19 and 37 specifically have been sequestered from genital tracts of young adults with EKC, indicating the possibility of sexual transmission.[25,26] Group D HAdV type 37, for example, has been isolated from sexually active men with adenoviral urethritis.[24] Additionally, Liddle et al discussed eight cases of individuals presenting with concurrent conjunctivitis and adenoviral urethritis.[23] Avolio et al also presented a case of two male patients with HAdV D37 associated urethritis and conjunctivitis, in which one of the spouses contracted adenoviral conjunctivitis via oculogenital contact. These cases highlight the importance of testing for the presence of adenovirus in clinical specimens collected from both urethral and conjunctival swab in men presenting with conjunctivitis, dysuria, and scant urethral discharge.[22]

Management

Due to the aforementioned HAdV characteristics and its interactions with host cells, HAdV has demonstrated a high likelihood of evading the immune response leading to infection. Additional research on its many modes of transmission contributes to the highly contagious nature of HAdV and dissemination into the community. Large-scale epidemics lead to high social and economic burdens, making health education in infected patients an invaluable tool to limit spread. Preventative methods require that patients exercise frequent hand washing with soaps and to keep hands dry, avoiding eye rubbing. Children are to be encouraged to stay home during the infectious phase to limit the spread of disease. Contact with infected towels, soap, bedding, door handles, etc. should also be avoided. Following resolution of the virus, bedding, and towels used by the infected individual should be washed thoroughly and exposed under sunshine (solar ultraviolet radiation) to further ensure elimination of the virus.[27] EKC outbreaks are also commonly spread through ophthalmology clinics, warranting the need to evaluate disinfection procedures for ophthalmic instruments. Methods of spread include tonometry probes, tips of contaminated eye drop bottles, and foreign body removal instruments. A study comparing the efficacy of hydrogen peroxide disinfection versus alcohol swabs determined that there was a more significant reduction in log growth using hydrogen peroxide. The use of disposable prisms is also an option, though many times this method is of limited use due to cost.[28,29] Because of these unique viral characteristics, ubiquity of HAdV, and its potential for epidemic, several treatment modalities have been investigated to establish an effective treatment protocol. However, at this stage, there is no FDA-approved antiviral treatment for HAdV infections.

Povidone-Iodine Irrigation

Though molecular iodine has long been established as an effective antiseptic agent, its formidable toxicity upon

contact to mucosal surfaces deterred it for use in clinical the clinical setting.[30] However, combining iodine with povidone allowed for this antiseptic to be safely and routinely used in the ophthalmic setting, and has even shown promise in the management of EKC affected individuals.

Povidone-iodine (PVI) is a broad-spectrum microbicide solution, which exists in multiple forms that are easily accessible, and a cost-effective disinfectant agent. Since its discovery, it has been routinely utilized in the medical field as an antiseptic agent for laboratory and surgical purposes. Furthermore, it has found much purpose in the ophthalmic setting as an effective disinfecting solution due to its proven toxicity against viruses, bacteria, parasites, fungi, yeasts, molds, and protozoans.[31] Diluted forms of PVI are commercially sold as Betadine (Alcon Laboratories, Inc., Fort Worth, TX 76134) in 5% and 10% concentrations and can be further weakened as medical use requires. It is critical to note that, unlike other antiseptics, PVI does not lose antimicrobial activity with decreased available iodine concentration in solution when a diluent is added.[30]

The mode of action requires the oxidation of pathogen nucleotides, amino acids, and proteins, damaging vital bacterial cellular mechanisms.[32] Additionally, in vitro investigation indicates that PVI impedes the host's inflammatory response to a viral pathogen by affecting both host and pathogen parameters.[33] This may give insight into how in-office PVI irrigation may alleviate inflammatory symptoms associated with EKC. Specific pathogen consequences include inhibition of production and release of exotoxins (such as α-hemolysin, phospholipase C, and lipase) and suppression of bacterial enzymes (such as elastase and ß-glucuronidase).[32]

Host factors involve modulation of antioxidant and free radical activity, inhibition of inflammatory effector cells and mediators (such as TNF-α and ß-galactosidase), inhibiting matrix metalloproteinase production, and enhancing healing signals via activation of T cells and macrophages.[32] Globally, PVI characteristics that make it ideal for clinical use include broad antimicrobial spectrum, lack of resistance, ability to penetrate biofilms, low cytotoxicity, suitable tolerability, and overall favorable risk/benefit profile.[32] Such versatility, ease of access, and ubiquitous use in antisepsis have been further promoted by biochemical characteristics of the compound. The combination of a synthetic carrier homopolymer (2-pyrrolidnone, 1-ethenyl-), which has no innate germicidal ability, and iodine forms PVI.[34] In aqueous form, free iodine is released into solution from the PVI complex, which is what provides the microbicidal activity.[32]

Studies have shown that PVI exhibits antimicrobial activity proportional to the concentration of free iodine released in any given solution of specified dilution, regardless of PVI concentration.[30] In addition to its well-documented antimicrobial activity, a study examining the virucidal efficacy of 0.01%, 0.1%, 1%, and 10% PVI demonstrated that 0.1% solution was actually the most effective against HAdV 3, as it maximized free iodine concentration.[30] Specifically, PVI formulations have been proven effective against non-enveloped human viruses including HAdV, although, it has been postulated to be adenoviral type dependent.[35,36]

PVI has been shown to demonstrate virucidal reductions for ocular HAdV types 3, 4, 5, 7, and 8 at 1–5 mins and types 37, and 64 at 15–60 mins for various concentrations.[36] This may indicate that time of exposure, not concentration of PVI, to disinfection is critical and that virucidal activity for PVI at different concentrations may require temporal consideration when evaluating specific virus types. Though PVI has been tested in vitro, in animal models, and clinically for its use in disinfection and wound healing for many decades, the use of a PVI irrigation in-office for EKC remains off-label.[32] The theory behind in-office PVI irrigation is to reduce viral load on the ocular surface and to decrease viral shedding. A commonly implemented protocol in clinical practice involves anesthetizing the affected eye(s), then instilling a pre-irrigation NSAID drop, followed by four to five drops of 5% PVI solution. The patient then rolls his or her closed eye(s) for 60 s to maximize exposure (including swabbing of the eyelid margins), followed by lavage of the ocular surface with sterile saline irrigation solution (Figure 1). Finally,

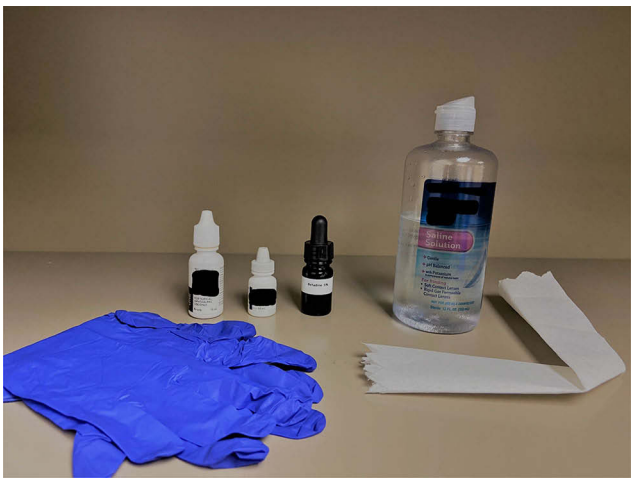

Figure 1 Set up for in-office povidone-iodine irrigation. From left to right: nitrile gloves, topical anesthetic, topical NSAID, betadine, 5% solution, saline solution, and folded paper towel for saline rinse.

a post-irrigation NSAID drop is instilled. Anecdotally, patients may report exasperation of their conjunctivitis symptoms for 12–24 hrs after this procedure; however, the overall risk/benefit consideration regularly tips the decision in favor of preforming PVI irrigation.[32]

Interestingly, Cheung et al have indicated that multiple types of adenovirus can be involved in a single outbreak and as PVI has proven viricidal activity in multiple ocular types of HAdV, it would be sensible to consider PVI irrigation to decrease colonization of the ocular surface in this disease picture.[37] The most powerful tool in limiting the severity of adenoviral conjunctivitis outbreaks includes reduction of viral shedding and limiting contamination of objects, workspaces, and surfaces in public places to avoid horizontal transmission, as mentioned previously in this manuscript.[38] Gargling or flushing with PVI has been postulated as an effective measure in disrupting the transmission of respiratory viral spread.[39] Hence, PVI irrigation can be a powerful tool to help in the reduction of transmission of adenoviral keratoconjunctivitis.

PVI has also shown value in treatment formulations. A large clinical trial for the use of 1.25% PVI ophthalmic solution in the treatment of pediatric conjunctivitis displayed efficacy in treatment of bacterial, chlamydial, and viral conjunctivitis.[40] Interestingly, a clinical trial looking at 0.5% PVI (in combination with artificial tears at pH 4.2 for enhanced tolerability) for the treatment of adenoviral keratoconjunctivitis found faster recovery from disease at two weeks, with three drops administered thrice daily.[34]

Antiviral Therapy

Antiviral activity against systemic HAdV infections has been thoroughly studied and paved the way for its more focused evaluation for the treatment of the ocular manifestations of this virus. Besides the aforementioned forms of keratoconjunctivitis, HAdV may also cause upper and lower respiratory tract disease, hemorrhagic cystitis, and gastroenteritis due to its propensity to infect mucosal epithelium.[3,41,42] Respiratory infection is typically mild and self-limiting in immunocompetent individuals, but in rare cases, severe respiratory infection and pneumonia may result in acute respiratory distress syndrome (ARDS). Additionally, in immunocompromised patients undergoing hematopoietic stem cell or solid organ transplantation, disseminated infections can be life-threatening, particularly in the pediatric population.[3] Despite thorough investigation on the role of antiviral treatment both systemically and topically, there remains no standard of care. Possible therapeutic benefits have been demonstrated through the use of antiviral drugs such as ganciclovir, ribavirin, and cidofovir.[41–44]

Ganciclovir (GCV), a synthetic nucleoside analog of 2′-deoxyguanosine, has been proven effective in the inhibition of the herpes family of viruses, specifically herpes simplex types 1 and 2, varicella-zoster virus, cytomegalovirus, and Epstein-Barr. In a series of experiments utilizing Syrian, immunocompromised hamsters infected with HAdV 5, GCV was able to suppress viral replication in the liver, a method that may involve the direct inhibition of DNA polymerase. It was proposed that GCV inhibited the advancement of viral infection into the late phase. Systemically, GCV was able to mitigate the effects of HAdV infection in these hamsters, decreasing the rate of mortality. This led to the investigation of GCV in the treatment of ocular infections of HAdV.[43,44] The ophthalmic gel form (ganciclovir 0.15%, Virgan®; Farmila-Thea, Milan, Italy) has been the standard of care for the treatment of acute ocular herpetic keratitis, yet it has not been standardized in the management of adenoviral keratoconjunctivitis, particularly since studies in human subjects are lacking.[43,44] Current research suggests, however, that with off-label topical use, GCV inhibits the replication of HAdV that leads to ocular infection. Several clinical trials have reported its efficacy.[43–46]

In one study, Huang et al investigated the antiviral activity of GCV against HAdV types 3, 4, 8, 19, and 37 using polymerase chain reaction (PCR) and concluded that there was a significant, dose-dependent inhibitory effect on those serotypes responsible for EKC.[46] Systemically, Bruno et al described the potential therapeutic effect of GCV in that the incidence of HAdV infections was significantly reduced in stem cell-transplant patients treated with GCV for human cytomegalovirus prophylaxis.[45]

Sun et al conducted a study utilizing a series of eye drops to treat active EKC infections, including GCV ophthalmic gel, interferon eye drops, a tobramycin-dexamethasone combo, and topical diclofenac sodium. In this study, interferon was administered with the purpose of inhibiting viral replication, while GCV was used for its antiviral properties. To improve efficacy and limit potential ocular side effects, such as inflammation, congestion, and edema, tobramycin-dexamethasone and diclofenac sodium treatments were also employed. This combination of drugs demonstrated a 91.76% cure rate in a 6-week treatment period, with low risk of side effects limited to transient corneal epithelial defects and elevated intraocular pressure. While EKC is often considered to be self-limiting, this study concluded

that the proposed treatment plan, specifically during the early phase of the disease, could markedly reduce the patient's symptoms, shorten the course of the disease, and lessen the risk of corneal complications.[27]

Valganciclovir is a pro-drug of GCV that inhibits replication of adenoviral genomic DNA via blockade of HAdV DNA polymerase. However, because HAdV lacks thymidine kinase, a known target for valganciclovir, it would likely become a challenge in the treatment of adenoviral keratoconjunctivitis.[47]

Ribavirin and cidofovir have also been shown to exhibit antiviral activity against HAdV in vitro. However, many of these systemic antiviral therapies lead to the risk of significant side effects. Cidofovir (CDV) is an acyclic nucleoside phosphonate and nucleotide analog of cytosine. It is converted by cells to its diphosphate form and binds to the HAdV DNA polymerase, causing viral DNA chain termination and viral inhibition.[13,44] Intravenous cidofovir is often used in transplant clinics with only mild efficacy. This is due to poor cellular uptake because of its phosphate group, leading to accumulation of the drug in the renal tubules and, when used systemically, leads to nephrotoxicity.[44,46] Locally, CDV may also cause ocular toxicity around the skin of eyelids and conjunctiva.[46] Similarly, ribavirin also results in poor systemic side effects and safety profile, associated with extravascular hemolysis, anemia, and bone marrow suppression. Due to these discoveries, it is necessary to determine an effective antiviral with a high therapeutic index for the treatment of HAdV associated infections.[46]

In animal models, CDV was administered utilizing topical and intrastromal inoculation three times per day for 20 consecutive days; the results displayed significant effectivity against HAdV type 5 when compared to the placebo group, reducing both viral shedding and the severity of subepithelial infiltrates. This study showed great promise in the future of cidofovir for the treatment of ocular HAdV infections in the future.[48] Additionally, early systemic administration of CDV in immunocompetent patients with HAdV pneumonia was an effective treatment strategy.[42] Due to the positive results in the aforementioned studies, CDV was tested as a prophylactic measure due to the epidemic nature of HAdV. Romanowski et al determined that antiviral prophylaxis with 1% and 0.5% concentrations of CDV significantly reduced viral replication of HAdV type 5 in animal models, giving promise to the use of CDV in prophylaxis.[49]

Despite favorable outcomes of cidofovir's antiviral activity in rabbit models, several studies discussed the significant side effects to the ocular surface, which is a potential limitation for therapeutic use. Gordon et al described the effects of topical cidofovir in uninfected animals, determining that there was consistent clinically significant ocular toxicity at a total dose exceeding 15mg over 10 days.[50] Significant eyelid redness and conjunctival hyperemia were also described in additional studies as well as nasolacrimal blockage and lacrimation.[50,51] Even at lower and presumably ineffective dosages, 3.5 mg of cidofovir continued exhibit significant ocular surface toxicity in vivo.[52]

Resistance to CDV is likely due to changes in amino acid sequence within the encoded DNA polymerase genes in resistant HAdV, which has been suggested to confer resistance of adenovirus to CDV. Drug resistance poses a significant challenge to the management of adenoviral keratoconjunctivitis in the clinical setting.[53] Romanowski et al were able to demonstrate that HAdV type 5 that are resistant to topical CVD therapy are less likely to constitute a significant challenge in management of adenoviral keratoconjunctivitis in immunocompetent patients. Drug-resistant viruses usually pose a minimal threat in immunocompetent patients, but CDV-resistant HAdV can retain their ability to replicate in permissive ocular epithelial cells.[54] Another major challenge to the use of CDV for treating adenoviral keratoconjunctivitis is its propensity to lead to toxicity, which manifests as persistent epiphora from lacrimal canalicular blockade.[53] As such, despite its potential, its high toxicity profile and poor bioavailability make CDV a less than ideal treatment option for the treatment of HAdV associated infections, both systemically and locally.

The solution to these challenges led to the investigation of brincidofovir (BCV), a lipid-linked derivative of CDV, which allows for cells to uptake the drug more readily when administered orally.[13,44,55] Following cellular uptake, the lipid component is cleaved by phospholipases, leaving CDV. This allows for similar antiviral efficacy as seen with CDV, but without the subsequent nephrotoxicity. Averbuch et al. reported successful use of BCV in the treatment of adenoviral infection in a patient with primary immunodeficiency whereas Florescu et al demonstrated that it was clinically beneficial in treating adenoviral infection in immunocompromised individuals who were at risk of disseminated HAdV infection.[56] It was suggested that BCV could be a potential anti-adenoviral therapeutic agent.[57] Though this drug shows promise, there is still a need for more conclusive research regarding the effectivity and safety profile of BCV systemically, as well as its

potential for the treatment of adenoviral ocular infections. Clinical development of this drug is ongoing, as there is yet to be an ophthalmic form.[13,44] When antiviral comparison is made, ganciclovir appears to be the most favorable in terms of antiviral activity and limited systemic or local side effects.[46]

Immunoglobulin (Ig)-Based Therapy

In 2001, Goosens et al discussed the antiviral activity of anti-Ad IgG on gene transfer to synovial fluid. This was attributed to the antibodies' ability to target adenoviral capsid proteins, subsequently inhibiting infection by the virus.[58] Topically, immunoglobulin (Ig) may offer the same effect on ocular tissue and prevent transmission and replication of the virus, to some degree. In addition to its antiviral properties, Ig has the added benefit of anti-inflammatory effects, which can aid in sub-epithelial infiltrate management.[59] Nwanegbo et al found that Ig was actually comparable to cidofovir in its antiviral activity. While cidofovir acts intracellularly to block DNA replication, Ig neutralizes the virus on the ocular surface. In comparison to cidofovir and saline titers, Ig was more effective during the acute phase of the infection.[59] It worked to aid in the clearance of the virus, shortening the duration of the infection, and thereby limiting the transmission of the virus. Additionally, Ig may be beneficial in prophylaxis to prevent clinical infections. Though both cidofovir and Ig were effective in this study, cidofovir demonstrated a significantly shorter duration of viral shedding. This is likely due to the mechanism of intracellular-mediated adenoviral DNA polymerase-blocking activities and prolonged tissue half-life after rapid uptake into cells. This study yielded promising results in the future of topical Ig use on ocular HAdV infections. The limitation lies in product consistency as Ig is derived from serum pooled by various donors, though anti-adenoviral efficacy appears stable over different lots.[59,60]

Topical Anti-Inflammatory Therapy

Corneal involvement in EKC occurs in approximately 80% of cases, varying in presentation as a superficial punctate keratitis, focal epithelial punctate keratitis, subepithelial infiltrate (SEI) formation, and reduced corneal sensitivity.[1,2,12,61] SEIs specifically will often manifest anywhere from one to three weeks following the acute phase of the infection. Histologically they are comprised of residual antigen and lymphocytic accumulations that adhere to stromal cells in the cornea.[62] This clinical finding may persist for months to years following resolution of the conjunctivitis, leading to subjective visual disturbances, such as decreased vision, photophobia, halos, and the development of irregular astigmatism. Due to their chronicity and visual impact, treatments including anti-inflammatory and immunosuppressive agents have been investigated to treat as well as prevent SEIs, though they often end up resolving without scarring or corneal neovascularization formation.[2,12,62]

Research demonstrates that mild corticosteroid treatment administered topically approximately three times per day can significantly improve EKC symptoms and, if used in the short term, acute phase of the disease, does not lead to significant ocular side effects. There is also additional benefit in the use of topical corticosteroids once the acute phase of the infection resolves, for the remaining, persistent SEIs.[2,63] While chronic corticosteroid treatment has been proven to reduce these findings, a significant challenge to this mode of treatment is the risk of complications of long-term use, including glaucoma and cataract formation.[64–69] Additionally, corticosteroid treatment of SEIs can result in a 17.5% recurrence rate and consequential, unsuccessful drug tapering.[70] If discontinued abruptly, these viral antigens continue to attract lymphocytes, causing persistence of SEIs.[62,66] Excimer laser ablation can be helpful in such cases.[63] In a study comparing topical loteprednol with dexamethasone, similar outcomes in SEI treatment were observed. This is significant because milder topical steroid forms, such as loteprednol, are known to have less risk of adverse effects.[71] However, it is important to note that short-term treatment with topical steroids of limited potency may also delay viral clearance.[72]

Nonsteroidal anti-inflammatory drugs (NSAIDs) are another alternative to corticosteroids, in that they are approved for topical, ocular use and exhibit anti-inflammatory effects without the substantial risk of glaucoma and cataract effect seen with steroid use. These agents work on the arachidonic acid pathway by inhibiting cyclooxygenase and, subsequently, the formation of prostaglandins, thromboxane, and prostacyclin. With specificity to ocular uses, they have been shown to be effective in cases of allergic conjunctivitis, alkali burns, herpetic uveitis, ocular trauma, and pre/post-operative cataract and refractive surgeries.[73–76]

Gordon et al were the first to investigate NSAID effects on adenoviral replication, specifically ketorolac tromethamine and diclofenac sodium ophthalmic solutions. During both the early and late phases of infection, the effect of NSAIDs

on viral titers did not differ from control groups, nor did it affect the duration of viral shedding. In contrast, prednisolone treatment was shown to prolong viral shedding.[73] As it pertained to sub-epithelial infiltrates, treatment with diclofenac or ketorolac did not yield a statistically significant reduction when compared to control groups, whereas prednisolone did. This study suggests that NSAIDs are not likely to have any clinically significant antiviral effects.[73]

It is important to note that even though NSAIDs offer a higher safety profile with long-term use in comparison to topical corticosteroids, they do not seem to be useful in cases of HAdV-associated conjunctivitis. They are also not without complication and associated with risk of corneal melt.[74]

Pseudomembranes are marked by fibrin rich exudation lacking blood or lymphatic vessels, while true membranes are formed by coalescence of the exudation over the substantia propria of mucous membranes; both are common in adenoviral keratoconjunctivitis and may hemorrhage upon removal.[1] Histopathological studies indicate the presence of fibrin, neutrophils, macrophages, effector lymphocytes, and activated dendritic cells in these films.[1]

Because pseudomembrane formation can present in severe cases of adenoviral keratoconjunctivitis in the setting of an intense inflammatory response (Figure 2), in-office removal of the pseudomembrane could be beneficial in preventing further complications of conjunctival fibrosis and long-term sequelae. Additionally, pseudomembrane manifestation along with SEIs necessitates the need for topical anti-inflammatory management.

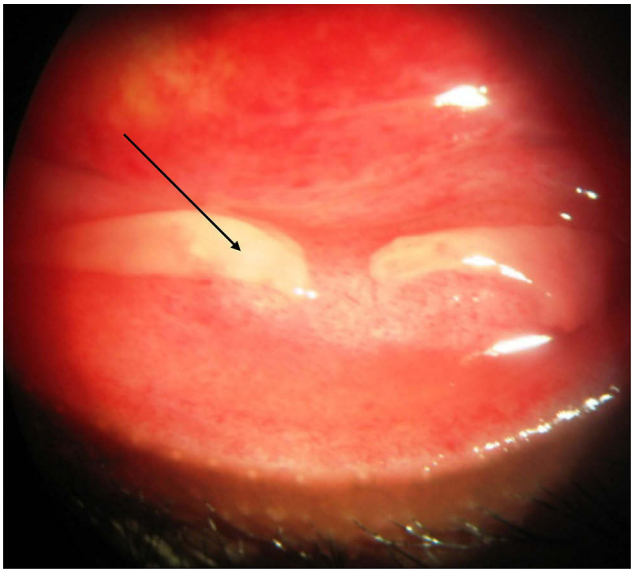

Figure 2 Presentation of an inflamed inferior palpebral conjunctiva with pseudomembrane (black arrow) in a patient with adenoviral keratoconjunctivitis.
Note: Copyright ©2018. Dove Medical Press. Reproduced from Chigbu DI, Labib BA. Pathogenesis and management of adenoviral keratoconjunctivitis. *Infect Drug Resist.* 2018;11:981–993.[2]

Immunotherapy and Cardiotonic Steroids

Cyclosporine, a non-steroidal immunomodulatory, was first developed in the 1970s as a novel drug to inhibit T cells both specifically and reversibly. Its first use was in whole organ transplants in attempts to avoid transplant rejection by tempering the host's own immune response.[77] Ocular use in HAdV keratoconjunctivitis should be considered when there is a need to dampen the immune response as in corneal complications of the virus, especially when there are contraindications of using corticosteroids or to limit associated corticosteroid complications.

Topical cyclosporine (both 1% and 2% concentrations) is an alternative option which, if used in the acute phase of adenoviral keratoconjunctivitis, is successful in both reducing the risk of developing corneal findings as well as the chronic treatment of persistent SEIs, with most cases resolving over a course of 3–4 weeks.[64,66,69,78] Okumus et al studied the efficacy of 0.05% cyclosporine (Restasis®, Allergan, Irvine, California, USA) once per day or once every other day, in treatment of SEIs secondary to adenoviral epidemic keratoconjunctivitis in cases persisting for more than three months. Patients in this study had also initially been treated with topical corticosteroids for several months with no regression, or who had to discontinue due to subsequent, elevated IOP. After one month of 0.05% cyclosporine treatment, 81.75% of eyes had cleared SEIs while the remaining 18.2% had decreased in number. No systemic or ocular side effects were observed. Few cases (11.12%) in this study resulted in recurrence of SEIs after discontinuing treatment.[69]

Cyclosporine is likely effective in these cases due to its action in the inhibition of T cell proliferation and activation, thereby reducing ocular surface inflammation.[77] It has been shown to be efficacious in various ocular diseases, such as vernal keratoconjunctivitis, ulcerative keratitis, Thygeson superficial punctate keratitis, herpes stromal keratitis, dry eye disease, superior limbic keratoconjunctivitis, and many others.[69,79-81]

Asena et al also evaluated treatment options for acute adenoviral keratoconjunctivitis using either topical 1% prednisolone acetate in conjunction with non-preserved artificial tears, topical 2% Cyclosporine A with non-preserved artificial tears, or non-preserved artificial tears alone. In

comparison to artificial tears alone, both the corticosteroid and cyclosporine groups exhibited improvement in symptoms as well as a shorter duration. Both the Cyclosporine A and prednisolone groups were also similarly effective in preventing the development of SEIs when used during the active phase of infection, suggesting possible prophylactic benefit.[72]

Tacrolimus is another immunosuppressive agent that also demonstrates anti-inflammatory activity. Like cyclosporine, tacrolimus' initial use was to prevent rejection in organ transplants. However, despite similar effects, tacrolimus and cyclosporine differ in their chemical makeup. Cyclosporine is a cyclic endecapeptide, in contrast to tacrolimus, which is a macrocyclic lactone. Both are calcineurin inhibitors, an enzyme necessary for T cell replication.[82,83] When cyclosporine and tacrolimus enter T cells, they bind to their respective immunophilins, which are important proteins that interact with calcineurin, and inhibit their action. Blocking calcineurin subsequently inhibits the transcription of several cytokines that are necessary to the immune pathway and response, particularly IL-2. This cytokine is integral in the maintenance, differentiation, and survival of $CD4^+$ T cells and $CD8^+$ T cells.[70,84-86]

Topical tacrolimus 0.03% has ophthalmic uses, mainly in the treatment of giant papillary conjunctivitis and vernal keratoconjunctivitis. With regards to its effect on HAdV keratoconjunctivitis, tacrolimus was more effective than dexamethasone in the reduction of SEIs, and subsequently in the improvement of vision and symptomology. This study is significant in that tacrolimus was not only superior to topical corticosteroids in the resolution of clinical signs and symptoms but also offered a lower recurrence rate and no significant rise in IOP as is sometimes seen with steroid use. Adverse effects were observed in 17.8% of patients using tacrolimus, manifesting as burning, redness, and foreign body sensation.[70] Generally, for SEIs that are resistant to tapering of corticosteroid, tacrolimus 0.03% was proven to be an effective corticosteroid-sparing agent.[87]

Another promising treatment for HAdV is adoptive T cell therapy. This involves the transfer of virus-specific T cells into Tcell-depleted patients to fight infection. HAdV-specific T cells are present in peripheral blood of healthy individuals in low frequencies; as a result, donor leukocytes were reportedly useful in patients with severe HAdV infection. HAdV-specific T cells play a significant role in viral clearance, and as such, adoptive transfer of HAdV-specific T cells would be an immunotherapeutic agent of immense benefit for patients at risk of disseminated adenoviral infection. The method of adoptive T cell therapy involves harvested leukocytes that are stimulated and expanded in vitro using peptide-MHC I tetramers, instead of using lymphocytes derived from the same donor as the transplant which yielded results as early as two weeks.[13,44] This therapy along with antiviral use appears to be synergistic and efficacious.[44]

Cardiotonic steroids digoxin and digitoxin have been suggested to offer a new strategy to target and suppress HAdV. Historically, these drugs have been used to treat heart failure for over 200 years. More recently, they have also shown efficacy in cancer treatments, in that treated patients demonstrated a lesser chance of relapse.[88] Hartley et al first noted its potential antiviral benefit, noting its efficacy against HAdV and herpesviruses.[89] This is due to the drugs inhibiting Na+/K+ ATPase on the cell surface, which leads to increased intracellular levels of NA+ and, subsequently, Ca++. Na+/K+ ATPase is an important cell signaling molecule, where binding with digoxin or digitoxin initiates multiple signaling cascades, influencing gene expression. These drugs also alter RNA splicing, which is necessary to HAdV replication. Preliminary data supports a concentration-dependent reduction in the number of infected cells and no apparent damage. Although there is known toxicity, particularly with long-term use of digoxin, the antiviral uses of cardiotonic steroids would be short term, negating the associated systemic complications. As such, these drugs seem to be efficacious against HAdV serotypes A-D and serve as potential treatment therapies for the treatment and prophylaxis of EKC.[88] Thus, repurposing of these cardiotonic steroids as an antiviral agent for short-term treatment of adenoviral keratoconjunctivitis as well as a prophylactic for use in individuals in close contact with patients with epidemic keratoconjunctivitis.[88] Furthermore, Marrugal-Lorenzo et al reported that mifepristone, a synthetic steroid drug, possesses anti-adenoviral properties via its interference with viral entry into the nucleus. As such, it could be repurposed for treating adenoviral infections.[90]

Combination Dexamethasone/PVI Treatment

The potential benefits of PVI as well as topical immunosuppressive therapies gave rise to the development of combined PVI/steroid ophthalmic solutions. The idea of combining

these elements is to employ the antiseptic properties of PVI in conjunction with symptomatic relief of inflammation, with the added benefit of reducing the risk and/or treatment of SEI formation and scarring.[2,52,72,91] Initial efficacy of combo PVI 0.4%/dexamethasone 0.1% dosed QID for five days was evaluated in a small study of nine eyes utilizing Rapid Pathogen Screening Adeno Detector-positive acute viral conjunctivitis.[91] The pilot study included both clinical (conjunctival injection and discharge) and serological (reduction of quantitative polymerase chain reaction titers and eradication of infectious virus as determined by cell culture with confirmatory immunofluorescence) endpoints.[91]

Combination treatment dosed QID for seven days has also been shown to improve clinical scores for scleral inflammation, ocular neovascularization, eyelid inflammation, friability of vasculature, inflammatory discharge, and epiphora as compared to treatment with 0.5% cidofovir, tobramycin/dexamethasone ophthalmic suspension, and balanced salt solution in rabbit models.[52] Moreover, PVI/dexamethasone combination has proven effective in reducing viral titers and delaying viral shedding.[52]

When comparing PVI/dexamethasone combination treatment with that of dexamethasone alone, combination drops not only increase recovery but also, reduce the risk of development of SEIs more effectively than steroids alone.[92] It is well documented that sole topical corticosteroid therapy has the risk of increased viral replication and prolonged shedding, further delaying the resolution of active infection. This significant treatment challenge is alleviated with the addition of PVI.[92]

In addition to the mentioned treatment benefits, combination PVI/dexamethasone ophthalmic formulation displayed a favorable safety profile and was well tolerated when administered for up to 14 days.[93] There was also no statistically significant effect on intraocular pressure, as is often associated with topical corticosteroid use. Reported side effects were limited to increased stinging upon instillation when compared to treatment with palliative artificial tears.[94]

Surgical Management

Surgical management is usually not required in adenoviral keratoconjunctivitis; however, it may be necessary in cases of significant fibrotic remodeling of the conjunctiva or sustained corneal scarring with visual consequence. Membranes that develop on the mucosal surface can be differentiated into pseudomembranes or true membranes, with the latter being clinically distinguished by induced bleeding upon denuding.[1]

Persistence of pseudomembrane can lead to subepithelial fibrosis of the conjunctival mucosa, symblepharon formation, and punctal occlusion.[1] Thus, rare cases may require repair of the fornix and associated lid anatomy defect (entropion or ectropion). Furthermore, streptococcal co-infection may be present in severe cases, with membranes that can precipitate corneal perforation and necessitate treatment.[95]

For patients with chronic adenoviral corneal opacification following resolution of acute infection, phototherapeutic keratectomy (PTK) can be an alternative option to other corneal surgeries or transplants. Corneal transparency can be compromised, or corneal irregularity may result with sequelae from the immune response to pathogen. Fortuitously, these scars are often superficial in nature by virtue of affecting the subepithelial layer. Transepithelial PTK low dose mitomycin C has shown benefit in such cases with reported improvements in photophobia, best corrected vision, and contrast sensitivity.[96] Furthermore, a decrease in coma, secondary astigmatism, and total higher-order aberrations have been noted after PTK for SEIs in adenoviral keratoconjunctivitis.[97]

Conclusion and Future Perspectives

Though many consider adenoviral conjunctivitis a disease of self-limitation, the economic burden on affected individuals, high contagion risk, and potential long-term visual complications require a treatment protocol. Studies have indicated that the inflammatory process affecting the cornea begins in the prodromal period of adenoviral infections, thus questioning the theory of self-limitation and adding a potential factor immediate therapeutic management.[98]

Dissemination of HAdV is also a significant health burden particularly in individuals with factors that put them at great risk of morbidity and mortality from adenoviral infection. These individuals include children, elderly, immunocompromised individual, patients with acute Graft versus Host disease, those on immunosuppressants, and so on. Because there are no FDA-approved drugs to treat HAdV infection, eye care providers use multiple pharmaceuticals off-label to manage HAdV ocular infection. Finally, the propensity for latent HAdV to become reactivated and easily transmissible warrants the need for additional research in developing an effective, prophylactic antiviral drug. New treatments under consideration include sialic acid analogs, cold atmospheric plasma (CAP), N-chlorotaurine, and even benzalkonium chloride (BAK). Sialic acid plays a role in initial attachment of fiber knobs in adenoviral virions while facilitating accumulation.[95] Sialic acid analogs have been

Table 2 Efficacy and Adverse Effects of Antiviral and Anti-Inflammatory Agents

Treatment/ Management	Efficacy	Adverse Effects
PVI irrigation	Off-label use for EKC; reduces risk of disease transmission	Dry eye symptoms, corneal epithelial damage/toxicity with repeated use. [104]
Cidofovir	Antiviral activity against HAdV5 exhibited in animal models. [105] Cidofovir 1% lowered the frequency of severe corneal opacities in patients with adenoviral keratoconjunctivitis.[64,106]	Narrow therapeutic index when used topically; high doses for greater than one week associated with rare cases of lacrimal canalicular blockade in rabbit models.[107]
Ganciclovir	3% ganciclovir reduced HAdV 5 replication and pathogenesis in animal models.[108] Ganciclovir is efficacious against HAdV types that cause EKC.[46] Ganciclovir ophthalmic gel treatment prevents complications in adenoviral ocular infection. [109]	Transient blur following instillation, eye irritation, punctate keratitis, conjunctival hyperemia.[108]
Brincidofovir	Brincidofovir has antiviral activity against adenoviruses. [55, 105, 110–113]	Mild gastrointestinal tract upset, asymptomatic and elevated levels of serum transaminases[114] diarrhea, acute graft versus host disease, abdominal pain, nausea/vomiting, decreased appetite, peripheral edema, hyperglycemia, hypokalemia, rash, fatigue, fever.[115]
Topical corticosteroids	Relief of EKC symptoms and Persistent adenoviral SEIs.[2,63]	Glaucoma and cataracts.[116]
Topical cyclosporine	Effective against persistent adenoviral SEIs.[66,69,117–119]	Transient or long-lasting burning sensation;[120] ocular pain/ irritation, redness; eyelid swelling in Steven Johnsons patients.[121]
Topical tacrolimus	Superior to dexamethasone in reducing symptomology and SEIs[70] as well as a safe and effective treatment of adenoviral SEIs.[87,122,123]	Transient burning sensation.[124]

theorized to block sialic acid-containing glycans which act as cellular receptors as a topical treatment.[95,99]

CAP is of use in dermatological disease and chronic wounds and has demonstrated adenoviral type-dependent antiviral effect that may be of benefit.[100] N-chlorotaurine, an endogenous antimicrobial agent, has been shown to shorten duration of illness and is well tolerated in in vitro and in vivo experiments; however, Phase II clinical trials were prematurely ended due to inability to meet primary and secondary endpoints.[101] These endpoints included clearing of bulbar conjunctiva, eradication of virus from tear film, fellow eye involvement, reduction of SEIs, and clearing of vision.[102] BAK is a commonly found preservative in ophthalmic formulations typically present as 0.01% concentration. Studies prove the effectivity of BAK as an antiviral agent against adenovirus in concentrations higher than 0.1%; however, note the disadvantage of ocular toxicity from the known disinfectant.[103]

Future considerations in the management of adenoviral keratoconjunctivitis should require consideration of antisepsis and mitigation of sequelae from the host inflammatory response. Furthermore, special consideration for persistent latent HAdV subtypes and immunocompromised individuals is required. Identification of exact mechanisms that underlie the adaptive immune response in adenoviral infections is prudent to the development of novel therapeutic sources. However, the lack of animal models that accurately mimic complexity of human ocular anatomy while also illustrating proper replication and infection of human adenoviruses can prove decelerating for new discovery.[95] Table 2 highlights the efficacy and adverse effects of antiviral and anti-inflammatory agents discussed in this review.[2,46,55,63,64,66,69,87,104-124] In summary, there are several challenges regarding the treatment of adenoviral keratoconjunctivitis. Though there are solutions to some

Table 3 Challenges and Solutions in the Management of Adenoviral Keratoconjunctivitis

Challenges	Potential Solutions
High likelihood of transmission and epidemic spread/burden	Health education in infected individuals and effective disinfection/prevention protocols
Persistent HAdV secretion in the tears	Further research regarding the development of a prophylactic antiviral agent
Reactivation of persistent latent HAdV in the host	Prevention of spread, treatment of immunocompromised individuals
Group D HAdV can cause oculogenital infection	Appropriate testing for HAdV subtype from urethra and conjunctiva in men
Duration of symptoms and transmission of EKC	Antivirals: ganciclovir, cidofovir, PVI irrigation
Poor bioavailability and high toxicity of cidofovir	Lipid-linked derivative brincidofovir and potential development of ophthalmic formulation
Development and/or persistence of SEIs	Topical corticosteroid therapy
Side effects of long-term corticosteroid use (ie, elevated IOP and cataract formation)	Immunotherapy such as topical cyclosporine or tacrolimus
Corticosteroids prolonging viral shedding	Combination PVI/dexamethasone ophthalmic solution
Conjunctival or corneal scarring	Pseudomembrane removal, PTK

of these issues, more research is required to determine a standard protocol (Table 3).

Disclosure

The authors report no financial affiliations or conflicts of interest in this work.

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