The Evolution of Antiviral Therapy for External Ocular Viral Infections Over Twenty-five Years

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Purpose. To review the past 25 years of the evolution of antiviral therapy for the treatment of common external ocular viral infections (herpes simplex virus type 1, varicella-zoster virus, and adenovirus). Methods. A broad-based literature review in the fields of virology, antiviral research, and ophthalmology will be carried out. The pathogenesis of the major external ocular viral infections and history of antiviral development will be cited. Important conceptual breakthroughs as well as historical landmarks will be emphasized. Results. The successful development of effective antivirals to treat the most common external ocular viral infections have dramatically reduced morbidity and sight loss. The immune pathogenesis of herpetic stromal keratitis is better understood. Conclusions. Remarkable progress in the development of antiviral therapy has occurred over the past quarter century. Future needs include improved antivirals and immunomodulators and vaccines to prevent and treat herpetic ocular infections and adenovirus keratoconjunctivitis.

Key Words: Antiviral—Herpes simplex virus—Varicella-zoster virus—Herpes zoster ophthalmicus—Adenovirus—EKC.

HERPES SIMPLEX OCULAR INFECTIONS

Herpes Simplex Epithelial Keratitis

By 1975, the antiviral treatment of live virus replication associated with herpes simplex keratitis was well established. The major historical breakthrough had occurred in 1959 when William Prusoff first synthesized a new anticancer drug, idoxuridine (IDU) (Fig. 1). Although it proved too toxic for systemic use in cancer patients, the antiviral strategy to differentially block DNA synthesis of intracellular herpes simplex compared to its host cell proved to be “the magic bullet.” IDU became the first antiviral drug to successfully treat a human viral infection when, in 1962, Herbert Kaufman demonstrated that topical therapy of herpetic epithelial keratitis with IDU led to rapid healing of corneal lesions in rabbits and patients. The mechanism of action was based on the uptake of IDU in place of the natural base, thymidine. Inhibition resulted from saturation of critical viral enzymes, thymidine kinase (TK) and DNA polymerase (pol); incorporation of phosphorylated IDU to form abnormal viral DNA; and translation of defective viral proteins. Clinical success was achieved in the eye because frequent dosing of topical IDU delivered directly to the target replicating herpes simplex virus (HSV) attained virucidal levels on the corneal surface. By 1975, IDU was the treatment of choice for herpetic epithelial keratitis worldwide. However, the shortcomings of topical IDU therapy: significant toxicity (superficial punctate keratitis, chemical conjunctivitis, and punctal occlusion) and frequent hypersensitivity reactions, limited its usefulness. As an insoluble agent, it had no therapeutic effect on herpetic stromal keratitis or iritis. Today, IDU is used infrequently in developed nations because it has been replaced by better drugs. However, it remains effective and is used in developing nations where cost issues are critical.

In the mid-1970s, several promising strategies to treat HSV epithelial keratitis failed. These approaches included interferon inducers, long acting, slow-dissolving IDU inserts (Ocuserts; Alza Corp, Palo Alto, CA, U.S.A.), cryotherapy, and photodynamic inactivation with light-activated dyes.

In 1976, vidarabine (Ara-A) was introduced as the second antiviral for topical therapy of HSV epithelial keratitis. It is a purine nucleoside analog to adenine (Fig. 2). The mechanism of action includes inhibition of TK, DNA polymerase, and DNA chain termination. Clinical trials demonstrated equivalent efficacy to IDU against HSV epithelial keratitis. Like IDU, it is relatively insoluble and demonstrates a similar toxicity profile. It is used mainly today by health maintenance organizations seeking cost-savings and in rare cases of hypersensitivity reactions to trifluridine (TFT).

In 1980, TFT was introduced as a major improvement over previous topical antivirals. It is a thymidine analog similar in structure to IDU but has three fluorine atoms at the five methyl group of the pyrimidine base (Fig. 2). Its mechanism of action is similar to the other nucleoside analogs, IDU and Ara-A. Clinical trials demonstrated superiority to IDU and Ara-A, especially in the presence of topical steroid. After frequent topical instillation, TFT penetrates the cornea to produce therapeutic levels in the aqueous. Topical toxicity is mild and includes superficial punctate keratitis, chemical conjunctivitis, punctal occlusion, and rare hypersensitivity reactions. For the past 20 years, TFT has proven successful as the topical antiviral of choice in the United States for the treatment of herpetic epithelial keratitis. TFT also provides excellent antiviral coverage when combined with a topical steroid in the treatment of the “immunogenic” herpetic stromal keratitis and iritis. True biochemical resistance is very rare, as trigeminal ganglionic latency guarantees that each reactivation event produces “antiviral-naive HSV virions” at the peripheral ocular site. Failure to obtain a positive clinical response (i.e., resolution of corneal dendrites and/or geographic ulcer) with TFT usually means poor patient compliance and/or an incorrect clinical diagnosis. The out-of-pocket costs for uninsured patients ($79.00/5-mL bottle; U.S. dollars) is a major impediment to compliance. TFT will remain the topical agent of choice in the United States for the foreseeable future.
In 1982, acyclovir (ACV), an exciting, breakthrough drug for the treatment of all herpes simplex (HSV-1, HSV-2) and varicella-zoster infections, became available in the United States. ACV is a purine analog to guanine with its deoxyribose ring broken open (Fig. 2). ACV represents a second generation antiviral that is specific for HSV-infected cells only. This selectivity of antiviral action significantly reduced host cell toxicity; and, for the first time, an antiviral agent could be administered orally and intravenously to treat serious systemic HSV simplex infections (encephalitis, genital herpes, etc.) in immunocompetent and immunosuppressed patients. The mechanism of action of ACV is as a nucleoside analog that blocks critical HSV enzymes (TK, DNA polymerase) and also functions as a DNA chain terminator. ACV readily penetrates the cornea after topical administration to produce virucidal levels in the aqueous. ACV demonstrates significantly less ocular toxicity (superficial punctate keratitis, punctal occlusion) than any other topical antiviral (TFT, Ara-A, and IDU). ACV ointment, 3% five times a day, is an extremely effective topical antiviral for the treatment of herpes epithelial keratitis; and, outside of the United States, it remains the drug of choice. ACV (400 mg T.I.D.) or equivalent prodrugs, valacyclovir or famciclovir, 9 may be administered orally as an alternative to topical therapy for the treatment of herpes epithelial keratitis. After systemic administration, toxicity is rare but normal renal function is required to excrete the drug. Therefore, patients on long-term ACV suppression therapy should have their renal function monitored (serial blood urea nitrogen, creatinine).

Ganciclovir (1989), foscarnet (1991), and cidofovir (1996) (Fig. 2) are other FDA-approved antiviral agents that are effective when administered systemically against HSV but that are not commercially available for topical therapy of HSV-1 epithelial keratitis. Ganciclovir ophthalmic gel 0.15% is currently in clinical trials in Europe. Brivudin, another thymidine nucleoside analog (Fig. 2), is also effective as a topical agent against HSV-1 epithelial keratitis but is only available in Europe.

After 25 years of antiviral development, we currently have excellent topical antivirals (TFT, ACV) for the treatment of HSV-1 epithelial keratitis. Antiviral resistance is not a clinical problem because of the role of HSV-1 ganglionic latency in recurrent keratitis. Nevertheless, ophthalmology would be well served with the development of newer topical antivirals that are more potent, less toxic, and cheaper. Infrequent dosing would provide for improved patient convenience and better compliance. Finally, research to develop antivirals other than nucleoside analogs to inhibit HSV-1 is worthwhile and ongoing (e.g., ribonucleotide reductase...
I. Nucleoside Analogs

A. Pyrimidines (Thymine, Cytosine, Uracil)

- Idoxuridine (T) (IDU) 1963
- Trifluridine (T) (TFT) 1980
- Brivudin (U) (BVUDU) 1992
- Sorivudine (U) (BVaraU) 1993 (Japan)

B. Purines (Adenine, Guanine)

- Vidarabine (A) (Ara-A) 1976
- Valacyclovir (G) (VACV) 1995
- Acyclovir (G) (ACV) 1982
- Ganciclovir (G) (DHPG) 1989
- Famiciclovir (G) (FMV) 1994
- Penciclovir (G) (PCV) 1994

II. Novel Antivirals - Broad Spectrum

- Foscarnet (PFA) Phosphonate Antagonist 1991
- Cidofovir (S-HPMPC) Acyclic Nucleoside Phosphonate 1996

FIG. 2. The chemical structures of antivirals used in ophthalmology. The single letter within the parentheses represents the natural base (A, adenine; T, thymine; G, guanine; U, uracil) for each antiviral nucleoside analog. The year indicates date of FDA approval.

Herpetic Stromal Keratitis/Iritis

Unlike herpetic epithelial keratitis with many therapeutic options, herpetic stromal keratitis (HSK) remains the major blinding form of herpetic ocular infection with fewer successful therapeutic options to date. The clinical distinction between herpetic epithelial disease (dendritic and geographical ulcers) and stromal disease associated with iritis was well understood by the early 1970s. The role of live HSV-1 in herpetic stromal disease and iritis was debated because of the demonstration of HSV particles in necrotizing keratitis and the recovery of live virus from the aqueous. However, there was general acceptance of Jone's Immunological Blotter Theory that HSK and iritis were principally host immune and inflammatory responses to HSV antigens deposited in the stroma, endothelium, iris, and trabecular meshwork after HSV-1 epithelial keratitis. Clinical observations of the day supported this theory of HSK/iritis—i.e., no concurrent epithelial dendritic or geographic lesions, no live HSV-1 by tear
film culture, and a positive clinical response to topical steroid therapy.

Research to better understand the pathogenesis of HSK has been aggressively pursued using animal models of HSV corneal infection over the past quarter century. Important factors appear to be immune complexes formed between HSV antigen and circulating anti-HSV antibodies, cell-mediated immunity and a cytokine-mediated inflammatory cascade, and viral “molecular mimicry.” Although cell-mediated immunity is demonstrated by the role of CD4+ helper T cells, interleukin-2, interleukin-10, and gamma-interferon, molecular mimicry is suggested by a late HSV-1 structural gene (UL 6) that produces a protein identical to a host cell protein with the same gene sequence.

Despite the apparent clinical benefits of topical steroid therapy for HSK and iritis, the mid-1970s were characterized by a continuation of the “The Steroid Wars,” which began in the 1950s with the introduction of topical corticosteroids into ophthalmic care. The influential West Coast School, led by Phillip Thygeson of the prestigious Proctor Foundation (UCSF, San Francisco, CA, U.S.A.), was unalterably opposed to the use of topical corticosteroids in any herpetic eye infection, including the “immunogenic” HSK and iritis. In contrast, the East Coast School led by Kaufman, Pavan-Langston, Laibson, and Nesburn favored a judicious use of topical steroids in conjunction with an antiviral cover for “appropriate” cases of HSK and iritis. These scientific differences were finally resolved 40 years later by the Herpetic Eye Disease Studies (HEDS I & II) in favor of the East Coast School.

The HEDS I study demonstrated the value of a 10-week course of topical corticosteroid therapy (1% prednisolone phosphate) combined with topical antiviral cover (TFT) to treat HSK. Compared to a placebo control, the combined therapeutic regimen demonstrated reduced persistence or progression of HSK, shorter duration of HSK, and no increased risk of recurrent HSK. Postponing the initiation of topical steroid therapy delayed the healing of HSK but did not adversely affect the visual outcome at 6 months. The HEDS I study also demonstrated no clinical benefit in treating HSK with a 10-week course of oral ACV as adjunct therapy to standard topical therapy of TFT and 1% prednisolone phosphate. Furthermore, the HEDS II study showed that after an episode of HSV-1 epithelial keratitis, a 3-week course of oral ACV (400 mg T.I.D.) failed to prevent the development of HSK (10% ACV vs. 11% control) or iritis in a 12-month follow-up period. The risk of HSK or iritis after HSV-1 epithelial keratitis was significantly higher (26%) in patients with a prior history of HSK or iritis.

Other smaller HSK treatment studies demonstrated flubiprofen to be effective when combined with antiviral cover. Cyclosporine A, a T cell inhibitor, demonstrated efficacy in experimental HSK models and in patients. A topical cover with oral ACV was shown to be as effective as topical ACV when combined with topical steroids in the treatment of HSK.

For treatment of HSV-1 iritis, the HEDS I study demonstrated a strong trend for clinical benefit (p = 0.06) with a 10-week course of oral ACV as adjunct therapy to standard topical therapy of TFT and 1% prednisolone phosphate. Unfortunately, the iritis study was stopped because only 50 of a targeted 104 patients were enrolled after 4 years of recruiting nationwide.

Prevention Strategies For Recurrent HSV Ocular Infections

Behavioral

In the mid-1970s, preventing recurrent herpetic keratitis was recognized as important to prevent sight loss from repeated corneal scarring. Topical antiviral prophylaxis with IDU and Ara-A was limited by significant local toxicity and frequent hypersensitivity reactions. A behavioral approach was favored in which each patient was advised to discover and avoid his unique clinical trigger(s) (e.g., stress, ultraviolet exposure, fever, hormonal changes). Unfortunately, for many patients, no specific triggers could be identified.

Long-term Antiviral Suppression Therapy

The breakthrough therapy in the prevention of recurrent herpetic infections was spearheaded by successful long-term antiviral suppression therapy with oral ACV to reduce the frequency and severity of episodes of genital and orofacial herpes. Long-term suppression proved to be safe and effective up to 5 years, with no emergence of resistant strains in immunocompetent patients. ACV suppression therapy (400 mg T.I.D.) also reduced the need for Cesarean section in patients with recurrent genital herpes and prevented reactivation of orofacial HSV-1 after laser resurfacing cosmetic plastic procedures. The success of ACV suppression therapy for genitl herpes has been duplicated with the produgs valacyclovir and famciclovir with more convenient dosing.

The value of ACV suppression therapy in preventing recurrent HSV-1 epithelial keratitis was suggested by natural history studies and after keratoplasty. Recent experimental studies also suggest the value of valacyclovir prophylaxis in current refractive procedures in the rabbit HSV-1 latency model.

The definitive National Institutes of Health-sponsored HEDS II study proved the value of long-term ACV suppression therapy for any form of ocular HSV (19% ACV vs. 32% control; p < 0.001), for HSV stromal keratitis (14% ACV vs. 28% control; p < 0.005), and for nonocular herpes and (primarily) orofacial (19% ACV vs. 36% control; p < 0.001). The most important result from the HEDS II study was the “paradoxical” finding that HSK, “an immunogenic disease,” could be significantly reduced by ACV suppression therapy (400 mg B.I.D.). This result provided, for the first time, a practical strategy to prevent this blinding form of ocular herpes.

How an antiviral could prevent recurrent HSK again raises the question of the role of live virus in this “immunogenic disease.” Three possibilities include direct antiviral inhibition of live HSV restricted to the stroma after ganglionic reactivation, corneal latency associated with limited viral replication and partial gene expression with limited production of viral antigens, and a persistent “low-grade” infection of HSV-1 sequestered in stromal keratocytes and endothelial cells. Additional research is necessary to clarify which mechanism is operative.

Similarly, infectious HSV-1 may play a role in recurrent iritis and trabeculitis as suggested by immunohistochemistry and positive cultures for aqueous samples. Replicating HSV-1 would explain the therapeutic role for ACV in the these “immunogenic” herpetic ocular diseases. Clinically, ACV suppression...
therapy has been shown to be effective in herpetic iritis\textsuperscript{52} and was suggested by a strong trend ($p = 0.06$) in the HEDS I study.\textsuperscript{31}

Vaccination

This broad topic is beyond the scope of a limited review of antivirals. The reader is referred to two excellent recent reviews on the subject by Bernstein and Stanberry\textsuperscript{53} and K rause and Strauss,\textsuperscript{64} which are summarized briefly. Prevention of recurrent herpetic disease by vaccination has been attempted since the 1920s. Early attempts included nonspecific stimulation of the immune system using live vectors (vaccinia and BCG) and autoinoculation to augment the patient’s own immunity. Later vaccine efforts (1930–1980) sought specific protection against HSV using heat, formalin, and ultraviolet-inactivated whole virus vaccines: Eli Lilly vaccine (U.S.A.), Lupidon vaccines (Germany), Skinner vaccine (U.K.), Dundarov vaccine (Bulgaria), Cappel vaccine (Belgium), Kutrova vaccine (Czech Republic), and Ivanovsky vaccine (Russia). Despite widespread uncontrolled trials with these inactivated whole virus vaccines, a therapeutic benefit (while claimed by many) has never been scientifically proven in controlled trials.

A promising approach to prevent recurrent HSV-1 would be to use a genetically engineered avirulent live vaccine to cause a primary infection and to specifically colonize the neuronal sites of latency with an impaired virus that would occupy the biological niche of wild type HSV-1 but that would be genetically incapable of reactivation to produce recurrent disease. A similar approach has been undertaken for VZV with the Varivax vaccine (M erck & Co. Inc., West Point, PA, U.S.A.), now part of a universal vaccination program to prevent or reduce the frequency of varicella. The success of this approach will be determined by the future incidence and severity of herpes zoster (HZ) and herpes zoster ophthalmicus (HZO) in today’s vaccinees.\textsuperscript{55}

Alternatives to a genetically-engineered avirulent live virus vaccine include a single cycle replication-impaired HSV-1 mutant (e.g., disabled infectious single cycle virus vaccine), non-HSV live vectors that express HSV genes (usually glycoproteins), subunit vaccines (HSV glycoproteins), and plasmid DNA vaccines that express HSV glycoproteins.\textsuperscript{53,54}

In summary, vaccine development (mostly for genital herpes) is ongoing by many pharmaceutical companies. Carefully performed controlled clinical trials is the only way to evaluate the merits of the different vaccine approaches to prevent recurrent herpetic infections.

Ganglionic Blockers

Although antiviral suppression therapy and vaccination offer the best chances for control of recurrent HSV-1 ocular infections, ganglionic blockers represent a novel approach. Once ganglionic latency has been established by wild type HSV-1, there is no known strategy (antiviral or otherwise) to eliminate the latent virus from its neuronal reservoir. However, blockade of HSV-1 reactivation was achieved in the monkey\textsuperscript{56} and mouse\textsuperscript{57} using 9-(4-hydroxybutyl)-N2-phenylguanine, a drug that inhibits the enzyme TK deemed essential for the efficient reactivation of HSV-1. Ganglionic blockade has also been achieved experimentally by manipulation of the autonomic nervous system using pharmacologic inhibitors. Alpha blockade with thymoxamine and corynanthine\textsuperscript{58} and beta blockade with propranololo\textsuperscript{59} were effective inhibitors of induced reactivation and ocular shedding of latent HSV-1 in murine and rabbit ocular models. The clinical application of ganglionic blockade as a successful strategy to prevent recurrent HSV infections remains to be demonstrated.

VARICELLA-ZOSTER OCULAR INFECTIONS

Over the past 25 years, significant gains have been made in the use of antivirals to treat systemic varicella, HZ and HZO. An alarming increase in the incidence and prevalence of varicella zoster (VZV) infections and HZO is attributed to diminished cell-mediated immunity (natural immunosuppression) associated with an ever increasing aging population, the expansion of the worldwide acquired immune deficiency syndrome (AIDS) epidemic, and an overall increase in the number of cancer patients. Furthermore, therapeutic immunosuppression associated with the explosive growth of transplantation surgery, cytotoxic therapy for serious autoimmune diseases, and chemotherapy for cancer patients all diminish patient cell-mediated immunity and promote VZV infections and HZO. In 1976, the ocular signs of acute and chronic VZV infections were well described as dermatomal skin vesicles, ulcerative blepharitis, conjunctivitis, epithelial dendrites, stromal infiltrates, iridocyclitis, secondary glaucoma, cataract, neurotrophic cornea, and postherpetic neuralgia, but there were very limited therapeutic options.\textsuperscript{6} Varicella hyperimmune globulin was recommended for at-risk patients with leukemia and other malignant diseases. The early available topical antivirals 0.1% IDU and 3% Ara-A demonstrated no therapeutic effect on the corneal dendrites observed during acute varicella or HZO. Intravenous Ara-A was used sparingly in high-risk immunocompromised patients to prevent disseminated zoster, but its effectiveness was limited by its insolubility and systemic toxicity. Systemic and topical corticosteroids were the most used drugs for the treatment of HZ and HZO before effective antivirals. The medical community was divided then as it is now as to the value of systemic steroids to reduce acute and chronic pain associated with inflammation. Topical steroids were favored by some ophthalmologists to reduce ocular inflammation associated with keratouveitis, but The West Coast School, in a doctrinaire manner, opposed the use of topical steroids to treat HZO as it had for HSV-1 stromal keratitis in the previously described “Steroid Wars.”\textsuperscript{56}

In 1982, the introduction of ACV antiviral therapy ushered in a dramatic new era of effective therapeutic options in the treatment of acute VZV systemic and ocular infections. Although there are conflicting claims about the value of topical ACV in the treatment of VZV epithelial keratitis,\textsuperscript{60,61} the use of oral ACV has revolutionized the treatment of HZO, a difficult and sometimes blinding disease. In 1986, a landmark controlled clinical trial by Cobo et al.\textsuperscript{62} established specific guidelines for the successful treatment of acute HZO. Clinically, ACV promoted a rapid resolution of existing skin lesions, prevented new lesion formation, and facilitated rapid resolution of VZV shedding and a rapid cessation of acute neuralgia. It reduced episcleritis, dendritic keratitis, and iritis during the acute phase, as well as subsequent chronic stromal keratitis. Unfortunately, ACV had no effect on neurotrophic keratitis or postherpetic neuralgia. Although a single study questioned its value in HZO,\textsuperscript{63} others confirmed it.\textsuperscript{64} ACV has been over
whelmingly endorsed by ophthalmologists and has become the standard of care for HZO in the past 15 years. ACV plays an essential role in the treatment of HZO in patients with AIDS and other immunocompromised patients. The natural history of the disease has been altered to create a chronic disease with persistent infectious VZV associated with dermatitis, keratitis, iritis, and frequent clinical recurrences. In immunocompromised patients, intravenous ACV has replaced the less effective and more toxic vidarabine as the agent of choice. Chronic ACV therapy in AIDS patients has led to the emergence of TK-negative ACV-resistant VZV isolates that have been treated successfully with intravenous foscarner.

The introduction of the produgs famciclovir (1994) and valacyclovir (1995) further enhanced the therapeutic options for the treatment of HZO. After oral administration, famciclovir is converted to its active form, penciclovir, and valacyclovir becomes ACV (Fig. 2). Enhanced bioavailability for both drugs produces higher serum concentrations, which allows for more convenient dosing. Both valacyclovir (1 g T.I.D. × 7 days) and famciclovir (500 mg T.I.D. × 7 days) have demonstrated superiority to ACV in the resolution of acute pain in controlled clinical studies of HZ. Currently, the dosage regimens established in the zoster studies are recommended for HZO. Although famciclovir is approved for use in AIDS patients, early studies with valacyclovir in very debilitated AIDS patients were associated with a number of deaths from thrombotic thrombocytopenic purpura/hemolytic uremic syndrome. However, current recommendations include the use of valacyclovir in selected human immunodeficiency virus-infected patients.

The most potent antiviral ever developed for the treatment of varicella-zoster virus infections was sorivudine (50% inhibitory concentration 1,000 × ACV) that was withdrawn from the Japanese market in 1993 after 18 deaths in patients concurrently receiving 5-fluorouracil. Bromovinyluracil (BVU), a metabolite of sorivudine, inhibited the hepatic enzyme dihydroprimidime dehydrogenase, which normally catabolizes 5-fluorouracil. Without this enzyme, 5-fluorouracil serum concentrations rapidly rose to fatal levels. Although a recent controlled clinical trial in the United States demonstrated that once a day dosing (40 mg) with sorivudine was superior to ACV in treating HZ in immunosuppressed patients, the FDA has indicated that it will not approve this drug and Merck has discontinued its development.

In 1995, the introduction of Varivax (Merck), a live, attenuated VZV vaccine, represented the next major advancement (after oral antivirals) in the management and prevention of varicella-zoster systemic and ocular infections. Varivax was developed by Tagahashi in the 1970s from the Oka strain of VZV recovered from a 3-year-old child with natural varicella. The Oka strain was attenuated by serial passage through multiple cell lines and differs from other wild type VZV in its capsid structure and assembly. It was widely tested in Asia and was found to be safe, immunogenic, and highly protective (93–97% protection) against natural varicella. Universal vaccination is now recommended in the United States and other countries for all children over 1 year of age and for at-risk adolescents and adults. Clinical trials are currently underway to determine whether therapeutic vaccination with Varivax can boost cell-mediated immunity and antibody levels high enough to prevent zoster and HZO in the elderly with wild type VZV ganglionic latency. Clinical studies have shown that 5–10% of Varivax vaccinees develop mild varicella. The vaccine establishes ganglionic latency and can reactivate to produce a mild zoster. Important questions remain to be answered in the future. Will Varivax significantly reduce the incidence and severity of HZ and HZO in future decades? Will future sporadic cases of wild type varicella be more severe as they occur later in life in an adult population?

In summary, the important progress of the past quarter century includes the successful development of effective oral antiviral therapy to limit the ravages of HZ and HZO. Antiviral therapy will continue to play a vital role in the near future with an expected increase in the number of HZ and HZO cases, but universal vaccination is likely to ultimately reduce the number and severity of HZ and HZO cases in future decades.

ADENOVIRUS OCULAR INFECTIONS

By 1975, ophthalmologists were well aware of the challenges of treating local hospital- and office-based and community epidemics of adenovirus (ADV) ocular infections. The pathogenicity of ADV ocular infections ranged from mild cases of follicular conjunctivitis to more serious cases of epidemic keratoconjunctivitis. Currently, the dosage regimens established in the zoster studies are recommended for HZO. Although famciclovir is approved for use in AIDS patients, early studies with valacyclovir in very debilitated AIDS patients were associated with a number of deaths from thrombotic thrombocytopenic purpura/hemolytic uremic syndrome. However, current recommendations include the use of valacyclovir in selected human immunodeficiency virus-infected patients.

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of cidovir will depend on encouraging results (efficacy and safety) in future trials and a favorable marketing projection. In summary, compared to HSV and VZV ocular infections, significantly less progress has occurred in the past 25 years in the development of effective antivirals to treat ADV ocular infections. However, a greater interest by pharmaceutical companies coupled with improved in vitro and animal models for antiviral screening offers the promise of success in the future.

REFERENCES


