New therapeutic approaches to the alphaherpesvirus infections

Kevin A. Cassady and Richard J. Whitley

Suite 616, Ambulatory Care Center, The Children’s Hospital of Alabama, 1600 Seventh Avenue South, Birmingham, AL 35233, USA

The character of diseases caused by alphaherpesviruses has changed over the last decade. The severity of disease and the frequency of acyclovir resistance has increased with the increase in the number of immunocompromised patients. Compounding the trend towards more virulent herpes disease is the current emphasis towards outpatient management of many diseases. Much of the current antiviral research focuses on providing drugs with (i) improved oral bioavailability and pharmacokinetics which permit less frequent oral or topical dosing for suppressive treatment of herpes simplex virus (HSV) infections, (ii) different mechanisms of action for synergic effects in treating resistant HSV infections in the immunocompromised host and (iii) improved efficacy. Future antiviral agents will probably target enzymes or viral factors essential for infection or will inhibit other steps in the viral infection cycle, such as viral entry, protein synthesis or capsid assembly. Medications that augment the immune response constitute another pathway for combating herpes viral infections. Many of the newer experimental agents target essential processes unique to herpesvirus replication and, therefore, potentially have high selectivity.

Introduction

The alphaherpesviruses that produce disease in humans consist of herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2) and varicella zoster virus (VZV). The severity and character of viral diseases caused by these viruses have changed over the last decade, as indicated by the increasing incidence and morbidity of infection. With the introduction of acyclovir in the 1980s, physicians had a highly selective and effective treatment for these potentially devastating and/or debilitating viral diseases. The number of immunocompromised patients has increased over the last decade as a consequence of aggressive chemotherapy regimens, expanded organ transplantation and the rising incidence of human immunodeficiency virus (HIV) infection. With this change in disease pattern, some alphaherpesviruses have developed resistance to acyclovir as well as other nucleoside analogues. New medications are needed for the continued effective treatment of herpes infections especially in the immunocompromised host. This review will focus on new trends in the treatment of alphaherpesvirus infections including immunotherapy.

Herpes infections are ubiquitous. By the third decade of life, approximately 16–35% and 40–80% of the USA population are seropositive for HSV-1 and HSV-2, respectively. Varicella zoster virus infects over 90% of people by adulthood. The incidence and severity of herpesvirus infection, however, are changing, reflecting the increased exposure and altered expression of disease in both the normal and immunocompromised host.

Neonatal mortality from disseminated HSV disease and herpes encephalitis has declined from 70% to 40% since the development of acyclovir and vidarabine. A ntiviral treatment of disseminated disease in the newborn decreases the morbidity from 90% to 50% of survivors and reduces the severity of neurological impairment. Varicella immunoglobulin and acyclovir have reduced the complications from primary VZV infection and herpes zoster in the neonate and immunocompromised patient. Topical, oral and intravenous acyclovir are effective for treatment of mucocutaneous herpes infections. Furthermore, prophylactic treatment with intravenous or oral acyclovir decreases the incidence of HSV recurrence. With the emergence of acyclovir-resistant herpesviruses in immunocompromised persons, novel antiviral agents
are needed for continued effective treatment of associated diseases. Acyclovir inhibits DNA chain synthesis selectively in HSV-infected cells. Following enzymatic activation by a virus-specific thymidine kinase (TK), the nucleoside analogue is further phosphorylated by host enzymes to its active triphosphate form. Viral DNA polymerase has higher affinity for acyclovir-triphosphate and the drug concentrates in infected cells, reaching a level 40- to 100-fold higher than that in uninfected cells. As a result, acyclovir has a high selectivity and few side-effects when compared with most antivirals. A cyclovir resistance most frequently results from changes in the TK enzyme but can also involve changes in DNA polymerase. Resistant virus isolates usually have less TK but resistance can also result from changes in TK substrate specificity.

Varicella zoster virus also has a TK enzyme that phosphorylates acyclovir; however, VZV-TK has less affinity for the drug than does HSV-TK. Patients with VZV disease, therefore, require more frequent and higher dosages of acyclovir.

The fundamental cellular and molecular principles of viral infection of cells and host response provide a framework for examining the mechanism of action of antiviral agents. Current chemotherapeutic agents attempt to disrupt viral replication at different steps in the infection cycle (entry, protein synthesis, replication, assembly or exit) or by modifying the host immune response. This review will initially focus on nucleoside analogues currently under evaluation for the treatment of HSV and VZV infections. The second part of the review explores future directions in drug development and herpesviral research.

Nucleoside analogues

The nucleoside analogues represent the first and the most thoroughly evaluated class of antiviral drugs for therapy of herpesvirus infections. These agents disrupt the fidelity or efficiency of viral nucleic acid chain synthesis, thereby inhibiting viral replication. Much of the current antiviral research focuses on providing nucleoside analogues that have (i) similar activity to acyclovir but improved oral bioavailability and pharmacokinetics permitting less frequent oral or topical dosing for suppressive treatment of HSV infections, (ii) different mechanisms of action for synergic effects in treating resistant HSV infections in the immunocompromised host and (iii) improved efficacy. A summary of these drugs, their route of administration, dosing frequency, and side effects is provided in the Table.

Valaciclovir

Valaciclovir, the L-valyl ester prodrug of acyclovir, has good oral bioavailability and produces higher serum levels...
of acyclovir than comparable oral doses of acyclovir.\textsuperscript{12} A s expected with a prodrug, valaciclovir has the same mechanism of action as acyclovir and requires TK-dependent conversion of acyclovir to the monophosphate form. Valaciclovir is absorbed from the gastrointestinal tract and converted to acyclovir by intestinal and hepatic first-pass metabolism. Sixty-three per cent of the valaciclovir oral dose is absorbed and converted to acyclovir, compared with the 15–21% absorption of orally administered acyclovir.\textsuperscript{13} The prodrug is rapidly converted into acyclovir, with less than 0.5% of the parent prodrug detectable in the serum.\textsuperscript{12} Oral administration actually results in more efficient conversion of active prodrug into acyclovir than does parenteral dosing of valaciclovir.\textsuperscript{14} V alaciclovir has a similar safety profile to acyclovir, with mild neurotoxicity and severe nephrotoxicity in animals at single doses of 1 g/kg and 2–5 g/kg, respectively.\textsuperscript{12} Subchronic toxicity in rats and monkeys showed that obstructive nephropathy occurred with valaciclovir at chronic mid and high dosing over approximately 3 months.\textsuperscript{15} Clinical trials in humans, however, have shown that valaciclovir is very well tolerated and relatively non-toxic at dosages of up to 1 g tds. Patients receiving valaciclovir report vomiting, other gastrointestinal upsets and headache as the primary side-effects of the medication.\textsuperscript{16} Patients with HIV infection receiving high dosages (2 g qds) of valaciclovir for several months experienced increased gastrointestinal intolerance. Additionally, a few patients developed idiopathic thrombocytopenic purpura or thrombotic thrombocytopenia purpura in AIDS Clinical Trials Group (ACTG) trial 204 although the relationship of this drug to administration is unclear. Investigators in phase I trials found that valaciclovir produced less renal toxicity and neurotoxicity than high dose intravenous acyclovir.\textsuperscript{12} The improved bioavailability combined with a high therapeutic index make this a good oral drug for the treatment of VZV and HSV infections. Valaciclovir, however, is not effective in treating acyclovir-resistant infections.

Clinical trials have compared valaciclovir and acyclovir for the treatment of herpes zoster and recurrent genital HSV infections in immunocompetent patients. Patients with herpes zoster over 50 years of age treated with valaciclovir (1 g orally tds) for a week had less pain and less analgesics than participants receiving 5 days of acyclovir (800 mg five times a day).\textsuperscript{17} Extending the duration of treatment with valaciclovir from 1 week to 2 weeks did not improve outcome further. On average, valaciclovir-treated patients reported resolution of post-herpetic neuralgia (PHN) approximately 2 weeks earlier than patients receiving acyclovir (median duration of pain, valaciclovir = 38 days vs acyclovir = 51 days; P < 0.03).\textsuperscript{12} The two drugs had similar effects upon viral shedding and the healing of cutaneous lesions. Drug side-effects were similar in the treatment groups and included nausea, vomiting and headache. In summary, valaciclovir was as effective as acyclovir in the treatment of herpes zoster, resulted in statistically significant shorter duration of PHN and provided a more convenient dosing schedule. Valaciclovir has also been compared with acyclovir for treatment of recurrent genital HSV infection in immunocompetent individuals. Over 2800 patients enrolled in three randomized double-blind placebo-controlled trials comparing valaciclovir and acyclovir for the treatment of recurrent HSV. Patients entering the studies began medication within 24 h of developing symptoms. Investigators found that both valaciclovir (1000 mg or 500 mg orally bd) and acyclovir (200 mg orally five times a day) reduced lesion duration and viral shedding by approximately 2 days when compared with placebo. The two drugs also reduced the duration of pain by 1 day. A approximately 25% of the treated patients failed to develop lesions beyond the initial papule stage. Valaciclovir is as efficacious as acyclovir for the treatment of recurrent genital HSV and provides a more convenient dosing regimen.\textsuperscript{23}

**Famciclovir/penciclovir**

Famciclovir is a diacetyl prodrug of penciclovir with high oral bioavailability, rapid tissue distribution and a long intracellular half-life. Hydrolysis in the intestinal wall and first-pass metabolism in the liver remove both acetyl moieties. Oxidation of this deacetylated form converts famciclovir to penciclovir.\textsuperscript{18} Approxi-mately 80% of the drug is absorbed after oral dosing and drug absorption is unaffected by pH. Food delays drug absorption but does not affect the absolute plasma level. Penciclovir, like acyclovir, undergoes monophosphorylation by virally encoded TK and concentrates in infected cells. Host enzymes further phosphorylate the drug to the active triphosphate form, which inhibits the viral DNA polymerase. Penciclovir is sensitive to reductions or mutations in TK and is not indicated for the treatment of alphaherpesviruses resistant to acyclovir. Penciclovir has a 12-fold higher affinity for VZV-TK and a significantly longer intracellular half-life than acyclovir, permitting less frequent dosing. Penciclovir has approximately one-hundredth the potency of acyclovir in inhibiting DNA polymerase but by virtue of its high intracellular concentrations and long half-life, it remains an effective antiviral agent.\textsuperscript{19} A nimal toxicity profiles for this drug indicate that, like many nucleoside analogues, it is carcinogenic (causing murine mammary carcinoma) and may cause testicular damage.\textsuperscript{20,21} H uman data, however, do not support the animal studies. A ny testicular effect was studied in a group of 67 men with recurrent genital HSV (33 placebo recipients and 34 famciclovir recipients) treated for 18 weeks with placebo of famciclovir 250 mg orally once daily. The study found no difference between the groups with regard to proportion of dead, immotile or normal sperm.\textsuperscript{24} A safety analysis of humans who had received famciclovir showed that the drug, like acyclovir, is well
tolerated and non-toxic. Famiciclovir increases digoxin levels and causes nausea (4.5%), diarrhea (2.4%) and headache (9.3%) in some patients. The constitutional side-effects, however, were comparable to those experienced by placebo recipients. Penciclovir is not metabolized and is eliminated unchanged in the urine. Clinicians should reduce the dose in patients with moderate and severe renal impairment. In patients with a creatinine clearance greater than 60 mL/min, there is no need to change the dose (750 mg) or the dosing regimen (three times a day).

The Collaborative Famiciclovir Herpes Zoster Study Group has examined the efficacy of famciclovir compared with placebo or acyclovir for the treatment of herpes zoster in immunocompetent adults. Initial randomized placebo-controlled trials showed that famciclovir (500 mg or 750 mg tds) accelerated cutaneous healing by 1 day and shortened the duration of PHN (55–62 days in the famciclovir group, 128 days in the placebo recipients). Subsequent studies have shown that a 7-day course of famciclovir (500 mg tds) is as efficacious as a 7-day course of acyclovir (800 mg five times a day) for the treatment of herpes zoster in immunocompetent patients. A cyclovir- and famciclovir-treated patients had equivalent healing rates, duration of acute pain and drug side-effects. There was a trend towards a shorter period of PHN in famciclovir-treated patients younger than 50 years of age; however, this trend was not statistically significant. One subgroup analysis (patients treated within 48 h of rash onset) of patients over 50 years of age suggested that famciclovir is superior to acyclovir for relief of PHN; however, significant differences existed between the populations in the two treatment arms. A balanced randomized controlled trial is currently in progress to test famciclovir and valaciclovir for PHN (R. J. Whitley, personal communication). In addition, a head-to-head comparison of famciclovir and valaciclovir is currently under way comparing the efficacy of these two prodrugs for the treatment of zoster and VZV disease in humans. Famiclovir is currently licensed in the UK at a dose of 250 mg tds.

Placebo-controlled trials have examined famciclovir for the treatment and suppression of recurrent HSV lesions. Investigators found that half of the patients receiving famciclovir had less pain than the placebo group. Lesions healed 2 days earlier in patients receiving famciclovir. The 250 mg bd famciclovir dose proved superior to once-daily famciclovir dosing or placebo as suppressive therapy for recurrent HSV.

A nimal studies show a significant difference between famciclovir and valaciclovir in the treatment of experimental HSV-1 infection. Mice received ad libitum famciclovir or valaciclovir in their drinking water (1 mg/mL) at least 1 day after experimental infection with HSV-1. Famiclovir-treated mice had a decreased quantity of infectious virus present acutely, and a lower frequency of HSV-1 latency and reactivation later. The famciclovir-treated group experienced less weight loss, shorter duration of lesions, lower mortality rate (30% valaciclovir versus 0% famciclovir) and decreased quantity of infectious virus in skin and ganglia than the valaciclovir-treated group. None of the 15 famciclovir-treated mice that received treatment within 3 days of infection had a recurrence of HSV during the 3 months for which they were followed. In contrast, the majority of mice (13 of 16) treated with valaciclovir had reactivation of virus after discontinuation of therapy, even when therapy was started 1 day after infection. In a second study, investigators attempted to control the amount of drug administered and gave mice equal amounts (50 mg/kg) of famciclovir or valaciclovir by gavage and found similar results. A though the animal data are promising, human data are required to confirm these differences.

Sorivudine

Sorivudine (5-bromo-vinyl-arabinosyluracil), a halogenated nucleoside analogue currently in advanced stage clinical testing, is extremely active against VZV. The drug exhibits good antiviral activity against HSV-1. It has a slightly different mechanism of action from acyclovir: unlike acyclovir, sorivudine does not act as a DNA chain terminator or become incorporated in viral DNA. A virally encoded TK converts sorivudine to the monophosphate form, similar to acyclovir; however, a second novel viral encoded enzyme is required for the synthesis of the diphosphate form of the drug. Cellular enzymes further phosphorylate the drug to the active triphosphate moiety which inhibits DNA polymerase. The specificity of sorivudine for VZV and HSV-1 infections originates from this dual viral enzyme activation requirement. Herpes simplex virus type 2 does not have the enzyme required for this second phosphorylation step. The drug, therefore, has approximately 1000- and 70,000-fold increased activity in HSV-1- and VZV-infected cells, respectively, when compared with HSV-2-infected cells. A high oral bioavailability, a long half-life (permitting once-daily dosing) and a low toxicity profile make this another potential drug for the treatment of herpes zoster. The drug does have one significant dangerous side-effect of note, though. Bromovinyl uracil, a metabolite of sorivudine, inhibits dihydropyrimidine dehydrogenase, the rate-limiting enzyme in pyrimidine base metabolism, and leads to the accumulation of related uracil-containing drugs. Many cancer patients receiving sorivudine and 5-fluorouracil developed myelosuppression and died secondary to the decreased metabolism and accumulation of 5-fluorouracil. Sorivudine is contraindicated in persons receiving 5-fluorouracil because of this toxicity.

Phase III clinical trials testing sorivudine against placebo and acyclovir for VZV infections proved that the drug is well tolerated and as effective as acyclovir. Sorivu-
Cidofovir

Cidofovir (1-[[S]-((3-hydroxy-2-phosphonomethoxy)propyl]cytosine dihydrate), a novel acyclic nucleotide analogue, has been used to treat cases of acyclovir- and foscartern-resistant HSV as well as cytomegalovirus (CMV) infections. Betaherpesviruses are particularly susceptible to the drug. The drug has a similar mechanism of action to the other nucleoside analogues (acyclovir, penciclovir) but employs cellular kinases rather than viral TK to produce the active triphosphate form of the drug. A citraved cidofovir has higher affinity for viral DNA polymerase and therefore selectively inhibits viral replication. The drug is less potent than acyclovir in vitro but, in vivo, it persists in cells for prolonged periods, increasing the drug's activity. In addition, cidofovir has active metabolites with long half-lives (17–48 h), permitting once-weekly dosing. Unfortunately, cidofovir concentrates in kidney cells 100 times more than in other tissues and produces severe proximal convoluted tubule nephrotoxicity when administered systemically. A attempt to limit the drug's nephrotoxicity include co-administration of probenecid with intravenous hydration, synthesis of cyclic congener prodrugs of cidofovir and use of topical formulations. Cyclic cidofovir is a prodrug of cidofovir that undergoes intracellular conversion to cidofovir. In-vitro systems demonstrate that the activity of cyclic cidofovir is comparable to that of cidofovir. In mice infected with HSV-2 and treated for 2 weeks, cyclic cidofovir was as potent as the parent drug but produced 1/13th the amount of nephrotoxicity. Cidofovir has limited and variable oral bioavailability (2–26%) when tested in rats and therefore is administered intravenously.

Cidofovir is currently in phase II/III testing for treatment of CMV retinitis in HIV-infected patients and in phase I/II trials as a topical treatment for acyclovir-resistant HSV infections. Probenecid has been added to intravenously administered cidofovir because of significant nephrotoxicity in patients during the phase I/II studies. Two of five patients with HIV and asymptomatic CMV infection treated with cidofovir (3.0 mg/kg) experienced increased creatinine levels after 6–14 doses respectively. Patients receiving higher doses (10 mg/kg) experienced nephrotoxicity after two doses. A case report documented systemic treatment of an acyclovir-resistant HSV infection; however, the drug was discontinued in this patient because of impaired renal function. Most of the published data on cidofovir involve preclinical animal trials or in-vitro studies.

Topical cidofovir (0.2%) is as effective as trifluridine (1%) in reducing HSV-1 shedding and healing time in rabbits with dendritic keratitis. Other investigators have examined the role of topical cidofovir in treatment and prevention of HSV-2 infections in mice and guinea pigs. Animals infected with HSV were treated 6–24 h after infection with topical acyclovir (5%) or cidofovir (0.5–5%) three times a day. Cidofovir-treated animals had reduced viral shedding and decreased lesion development when compared with acyclovir recipients. The 5% topical solution of cidofovir proved significantly toxic to guinea pigs. Lower concentrations (0.3%, 0.5% and 1%) of cidofovir were more effective than 5% acyclovir. Moreover, these concentrations did not produce the same toxicity as 5% cidofovir.

Cyclobutyl compounds

Cyclobutyl compounds represent a new group of carboxylic nucleoside analogues that provide broad-spectrum antiviral protection in experimental and animal studies. Moreover these agents have in-vitro activity against resistant strains of HSV-1, CMV, HSV-2, VZV and HIV-1. The nucleoside analogues terminate DNA chain elongation. Broad-spectrum antivirals would benefit patients with multiple viral infections, namely HIV-infected persons with herpesvirus infections. Lobucavir is a member of the cyclobutyl class of drugs, recently tested in a placebo control phase II trials for patients infected with HIV and CMV. The drug exhibited linear kinetics at low doses, had good bioavailability (40%), and had a half-life of 2 h. The drug was tolerated as well as placebo. Only one of the 27 patients completing the study excreted
The peptides are being investigated as a topical approach. Chemicals such as phospholipids, detergents and amphiphilic peptides inhibit herpesvirus attachment and entry. The mechanism of action of apolipoprotein A-1 is not known. HSV-1 possesses a unique, ribonucleotide reductase (RR) enzyme, which converts nucleotides to deoxyribonucleotides in HSV-infected cells. Ribonucleotide reductase inhibitors (RRIs) block the production of deoxyribonucleotides. By decreasing the pools of deoxyguanosine triphosphate (dGTP) RRIs facilitate acyclovir binding and inhibition of viral DNA polymerase. RRIs have shown synergic effects with acyclovir in vitro and DNA polymerase mutants of HSV-1. Initial attempts to create peptidomimetic RRIs have met with mixed results. A gents with in-vitro activity frequently are too toxic in animal studies while the less toxic topical preparations do not have sufficient antiviral activity when tested in humans. A attempts are currently under way to develop RRIs with high selective activity and oral bioavailability.

**Newer approaches**

Antiviral medications could inhibit viral infections at any step in the infection process. Targets for antiviral development include herpesvirus attachment, entry, uncoating, protein synthesis/translation, replication, assembly and egress. Many of the newer experimental agents target essential processes unique to herpesvirus replication and, therefore, potentially have high selectivity. Medications that augment the immune response constitute another pathway for combating herpesviral infections. Recombinant cytokines, monoclonal antibodies, vaccines and interferon inducers complement current antiviral agents and produce synergistic activity with acyclovir in vitro against some herpesviruses. Most of these newer antiviral agents and immunotherapeutics are still in preclinical trial and are presented with descriptions of viral pathogenesis and theoretical mechanisms of action.

**Helicase/primase inhibitors**

Drugs that inhibit the uncoiling of DNA have been used as anti-tumour drugs and are currently being studied as possible anti-herpetic agents. Helicase proteins uncoil the genome and are necessary for DNA polymerase and RNA polymerase binding. Additionally, helicase proteins are important in DNA repair. Drugs that cause intra-strand cross-links prevent uncoiling and repair of DNA but also cause mutagenesis and cell damage. By targeting the unique viral helicase proteins and other proteins composing the DNA polymerase complex, investigators hope to minimize cellular damage. HSV-1 contains a helicase-primase complex composed of unique long proteins (ULs) 9, 5 and 52. Both UL 9 and UL 5 exhibit helicase activity, containing multiple conserved sequences necessary for activity and are very sensitive to mutations, making them good targets for antiviral development. Moreover, proteins analogous to UL 5 and UL 9 exist in other herpesviruses (HHV6) and have shared sequence identity, making these potential broad anti-herpes targets.

**Protease inhibitors**

Viral assembly, nucleic acid packaging and egress are incompletely understood. Viruses contain proteases, unique enzymes essential to viral capsid assembly, which cleave structural proteins. The protein encoded by UL 26 in HSV-1 acts as a serine protease and proteolytically processes itself as well as infected cell protein 35 (ICP 35), a nucleocapsid protein. ICP 35 associates with immature viral particles, acts as a ‘scaffolding’ protein for capsid protein modification and is critical for viral particle maturation. Temperature-sensitive ICP 35 mutant viruses fail to package DNA and produce immature, aberrant empty capsids. Recently investigators showed that di-isopropyl fluorophosphate (DFP), a serine protease inhibitor, inactivates the UL 26 protease irreversibly in a time- and dose-related manner by covalently binding to serine at the active site. Pharmaceutical companies are currently researching potential protease inhibitors for HSV as well as other herpes viruses (R. J. Whitley, personal communication).

**Ribonucleotide reductase inhibitors**

HSV-1 possesses a unique, ribonucleotide reductase (RR) enzyme, which converts nucleotides to deoxyribonucleotides in HSV-infected cells. Ribonucleotide reductase inhibitors (RRIs) block the production of deoxyribonucleotides. By decreasing the pools of deoxyguanosine triphosphate (dGTP) RRIs facilitate acyclovir binding and inhibition of viral DNA polymerase. RRIs have shown synergic effects with acyclovir in TK and DNA polymerase mutants of HSV-1. Initial attempts to create peptidomimetic RRIs have met with mixed results. A gents with in-vitro activity frequently are too toxic in animal studies while the less toxic topical preparations do not have sufficient antiviral activity when tested in humans. A attempts are currently under way to develop RRIs with high selective activity and oral bioavailability.
found that taurocholic and dehydrocholic acids inhibit HSV-2 replication in cell culture at concentrations that did not produce cell damage. Bile acids contain chemicals that disrupt and saponify fatty acids. These chemicals provide a potential topical therapy to reduce viral shedding and the duration and symptomatology of cutaneous HSV disease.

Imiquinod/quinolone immunomodulators

Imiquinod is a quinolone immunomodulator, recently tested in animals and humans, that stimulates the production of alpha interferon, tumour necrosis factor alpha, interleukin 1, interleukin 6 and granulocyte/macrophage colony stimulating factor. Interleukins (especially interleukin 1) help generate both local and systemic immune responses. Furthermore, some studies have shown that recombinant cytokines limit the duration of H SV-1 shedding. A lpha interferon reduces the nucleic acid pool in H SV infected cells and, in a double-blind placebo-controlled trial for recurrent genital H SV-infection in patients with H I V infection, decreased the duration of symptoms and H SV shedding. Interleukin 1, combined with macrophage colony stimulating factor and interleukin 2, protects relatively immunosuppressed newborn mice infected with lethal doses of H SV. By augmenting the immune response in newborn mice 1 day before H SV-1 infection, investigators found that 77% of mice survived, as compared with 20% of untreated mice.

Imiquinod is one of three new drugs in the quinolone immunomodulator family. The other members, imidazoquinolone S-28463 and R-842, are currently in preclinical studies. Imiquinod has broad antiviral and antitumour effect and has recently been used as an adjuvant for immunizations and as a suppressive agent for recurrent H SV infections. When imiquinod was added to an H SV glycoprotein vaccine, animals generated a greater antibody response and had a lower H SV recurrence rate. The 90 day cumulative H SV recurrence rate of the vaccine/imiquinod group compared with the imiquinod mono-therapy group was 2.8 compared with 33.8 (P < 0.001), respectively. A nimal studies provide an artificial framework for demonstrating in-vivo effectiveness but are not directly applicable to human disease. Cytokines have discrepant effects at different concentrations and therefore may not have the same beneficial effects outside of the laboratory. Although, interferon/cytokine therapy remains experimental, the field holds potential. Immunomodulators have a role as vaccine adjuvants and as supplemental therapy in patients with immunological disorders or resistant virus.

Monoclonal antibodies and vaccines

Antibodies directed against glycoproteins D and B benefit animals experimentally infected with H SV. Pretreated animals experience less frequent infections than the untreated group. Animals receiving monoclonal or polyclonal antibodies within 72 h of infection have less severe disease and lower mortality rates than untreated animals. Synthesis of a therapeutic human monoclonal antibody against H SV could provide protection if administered to newborns exposed to H SV perinatally. Vaccination of mothers is an alternative way of providing protective antibody to newborns. Currently, a live attenuated glycoprotein vaccine and a subunit recombinant H SV vaccine are being tested. A vaccine utilizing glycoproteins D and B and adjuvant stimulates antibody levels equivalent to natural infection and has recently been tested in a therapeutic vaccine trial. Genetically engineered herpesviruses have decreased virulence and may function as future vaccine- and drug-delivery agents. Vaccines against herpesviruses have the potential to prevent primary infection or decrease the incidence and severity of recurrent herpes infection.

The Food and Drug Administration recently approved the distribution of the live attenuated Oka/Merck varicella virus vaccine, V arivax, in the U S A. Numerous reviews on the varicella vaccine exist and the reader is directed to these for a more comprehensive discussion of the vaccine. Approval of the vaccine will undoubtedly change the epidemiology and character of V Z V disease in the U S A. The American Academy of Pediatrics has recommended the administration of the vaccine to children 12–18 months of age and to adolescents and adults with no prior infection. The vaccine can be safely administered with the measles, mumps and rubella vaccine and plans are currently under way for a combination vaccine. In adult vaccinees, immune responses wane much more rapidly than in children. It is not known if vaccination will result in less severe but more frequent adult disease or if breakthrough wild-type infections will produce severe disease. A preliminary study of Varivax in the elderly showed that it increased the immune response and may be an effective way of preventing or attenuating zoster in this population. The live-attenuated varicella vaccine is not yet approved for immunocompromised patients. Antiviral therapy and immunotherapy are still important methods for treating life-threatening varicella infections in this patient population. Further study of the live-attenuated vaccine and/or research on an inactivated varicella vaccine may provide a safe alternative vaccination or immunization schedule to protect this patient population.

Conclusion

Herpes infections and acyclovir-resistance are increasingly significant clinical problems in the immunocompromised patient population. Newer nucleoside analogues provide improved efficacy, easier administration, and in
some cases antiviral activity in acyclovir mutant viruses. Most of these agents represent variations on the success of acyclovir. Future antiviral agents will probably target enzymes or viral factors essential for infection and will inhibit other steps in the viral infection cycle, such as viral entry, protein synthesis or capsid assembly. Improvements in our knowledge of herpesvirus molecular biology will probably provide other antiviral targets.

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