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Antiviral Therapy for Herpesvirus Central Nervous System Infections: Neonatal Herpes Simplex Virus Infection, Herpes Simplex Encephalitis, and Congenital Cytomegalovirus Infection

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Abstract

Herpesvirus infections of the central nervous system (CNS) are a significant cause of morbidity and mortality, including long-term neurologic sequelae. Among the family of herpesviruses, the most significant CNS infections are due to herpes simplex virus (HSV) and cytomegalovirus (CMV). The onset of HSV CNS infection can occur in neonates as well as older children and adults. CNS infection associated with CMV occurs predominantly in the perinatal period, but may also be seen rarely in children and adults, especially in immunocompromised individuals. Although advances in antiviral agents have led to improved outcomes, there is still a need for more effective treatments.

INTRODUCTION

Central nervous system (CNS) infections due to viruses of the Family *Herpesviridae* have been a key area of concentration in the development and implementation of antiviral therapies since the 1970s. Though nearly all members of the Family *Herpesviridae* can cause CNS manifestations, this review focuses primarily on CNS infections caused by herpes simplex virus (HSV) and cytomegalovirus (CMV), including recent developments in antiviral therapy, current limitations, and areas for future advancement.

HERPES SIMPLEX VIRUS

HSV-1 and HSV-2 are members of the alpha herpesvirus subfamily, which are characterized by a short reproductive cycle, prompt destruction of the host cell, and the ability to establish latency in sensory ganglia (Whitley, 2004). HSV-1 and HSV-2 each have linear, double-stranded DNA genomes of approximately 152 kbp. HSV infections are common in humans, and acquisition early in life is associated with low socioeconomic status (Nahmias et al., 1990; Xu et al., 2007; Xu et al., 2006). Though CNS infections due to HSV are much less common, they are associated with significant morbidity and mortality in spite of antiviral therapy. CNS involvement in HSV infections can be categorized as neonatal HSV CNS disease when it involves neonates, and as herpes simplex encephalitis (HSE) in individuals beyond the neonatal period.

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Neonatal Herpes Simplex Infections

Neonatal HSV infections occur in approximately 1 in 3200 deliveries in the USA (Brown et al., 2003). The majority of cases are caused by HSV-2 (Kimberlin et al., 2001b). The risk of transmission is increased with primary maternal infection during the third trimester and can be decreased by cesarean delivery if HSV has been isolated from the cervix or external genitalia near the time of delivery (Brown et al., 2003). As reviewed by Kimberlin, 85% of neonatal HSV cases occur due to peripartum transmission, whereas 10% occur via postnatal transmission and only 5% are due to transmission *in utero* (Kimberlin, 2007).

Infants with intrauterine HSV infection are characterized by the triad of cutaneous findings (active lesions, scarring), neurologic findings (microcephaly, hydranencephaly), and eye findings (chorioretinitis, microphthalmia) present at birth. Though this triad describes the classic findings of congenital HSV infection, more subtle presentations can occur as well. Intrauterine HSV infection has been found to occur with both primary and recurrent maternal HSV infections (Hutto et al., 1987), although the risk from a recurrent infection is less.

HSV infection acquired in the peripartum or postpartum period can be categorized as skin, eye, and/or mouth (SEM) disease, CNS disease, or disseminated disease. By definition, SEM disease does not involve the CNS. Disseminated disease may involve the CNS along with multiple other organ systems including the liver, adrenals, gastrointestinal tract, and the skin, eyes, or mouth. Infants with CNS disease may have SEM involvement, but lack evidence of other organ system involvement. Of all infants with neonatal HSV infections, approximately 30% have CNS disease, while about 25% have disseminated disease (Kimberlin et al., 2001b; Whitley et al., 1988). Of infants with disseminated disease, approximately 60 to 75% will have CNS involvement (Whitley, 1990). Therefore, by combining these statistics, it can be approximated that 50% of infants with neonatal HSV infection will have CNS involvement.

The pathogenesis of CNS involvement in neonatal HSV infections differs depending on whether or not the infection is disseminated. Encephalitis associated with dissemination is due to hematogenous spread, whereas isolated encephalitis or encephalitis associated with only SEM involvement usually occurs due to retrograde intraneuronal transport of the virus (Whitley, 2004). This corresponds to the clinical presentations of disseminated versus CNS disease in that the blood-borne spread of disseminated disease presents earlier (9 to 11 days of life on average) and causes more diffuse brain involvement with multiple areas of hemorrhagic necrosis, while CNS disease occurring via slower axonal transport presents later (around 16 to 17 days of life) and typically causes more focal CNS involvement (Whitley and Roizman, 2004). CNS disease can also occur via hematogenous spread, and these cases typically present similarly to disseminated disease, with more diffuse CNS involvement and earlier onset of symptoms.

In the pre-antiviral era, infants with neonatal HSV infections had significant morbidity and mortality. Infants with disseminated disease had an 85% mortality by 1 year of age and only 50% of survivors had normal neurodevelopmental outcomes; likewise, infants with CNS disease had a mortality rate of 50% by 1 year of age with only 33% of survivors having normal neurodevelopmental outcomes (Whitley et al., 1980). The early era of antiviral therapy for neonatal HSV infection was marked by improved mortality with intravenous vidarabine as well as with standard dose (SD) intravenous acyclovir (30mg/kg/day in 3 divided doses). Vidarabine is an adenosine analogue, while acyclovir is an acyclic deoxyguanosine analogue. Acyclovir requires 3 stages of phosphorylation, with the first phosphorylation occurring via the viral thymidine kinase and the 2 subsequent phosphorylations carried out by cellular kinases. Acyclovir's triphosphate derivative is able to competitively inhibit viral DNA polymerase as well incorporate itself into viral DNA, causing chain termination. With the use of these agents, the 1 year mortality for disseminated disease improved to 50% with vidarabine

and 61% with SD acyclovir, while the 1 year mortality for CNS disease dropped to 14% for both vidarabine and SD acyclovir (Whitley et al., 1991). More recently, high-dose (HD) acyclovir has been shown to further improve these mortality figures. Using HD intravenous acyclovir (60mg/kg/day in 3 divided doses), Kimberlin demonstrated 1 year mortality rates of 29% and 4% for disseminated and CNS diseases, respectively (Kimberlin et al., 2001a). This study also showed that HD acyclovir improves morbidity for infants with disseminated disease (83% of survivors had normal neurodevelopmental outcomes) but not for infants with CNS disease (31% of survivors had normal neurodevelopmental outcomes).

Herpes Simplex Encephalitis

HSE occurs in approximately 1 per 250,000 to 500,000 individuals per year (Puchhammer-Stockl et al., 2001; Whitley and Roizman, 2001) and is considered the most common cause of sporadic, fatal encephalitis (Olson et al., 1967). There is a bimodal age distribution of the disease; most cases occur in patients 6 months to 20 years of age or in patients older than 50 years (one-third and one-half of all cases, respectively) (Whitley et al., 1982). HSE can occur as a primary infection (30% of cases) or it can be caused by a recurrent infection (70% of cases), and virtually all cases of HSE are caused by HSV-1 (Nahmias et al., 1982).

The pathogenesis of HSE is not completely understood. Initial animal studies of primary HSE infections defined possible routes of entry into the CNS, most notably the trigeminal and olfactory nerves (Johnson et al., 1968). As summarized by Whitley, the entry of HSV into the CNS via the olfactory tract is a plausible hypothesis based upon its anatomic distribution into the limbic system. Animal models show the olfactory tract to be a viable avenue for viral entry leading to focal infection in an area analogous to the medial temporal lobe in humans. There are also reports of electron microscopic evidence of the virus within this nerve tract in some human cases (Whitley, 2004). For HSE that occurs due to reactivation of latent HSV infection, peripheral reactivation with subsequent neuronal transport via the trigeminal or olfactory nerves has been suggested. However, the observation that recurrent herpes labialis, which is due to reactivation from the trigeminal ganglia, rarely results in HSE seems to conflict with this theory (Whitley, 2004). Definitive determination of the exact pathogenesis is lacking for HSE resulting from either primary or recurrent HSV infections.

If untreated, HSE mortality approaches 70%, and of those patients who do survive, significant neurologic morbidity occurs in nearly 97% (Kimberlin, 2007). Idoxuridine was the first antiviral agent studied clinically for its efficacy in HSE, but it was found to be both ineffective and toxic (Boston Interhospital Virus Study Group, 1975). Vidarabine was shown to be more tolerable than idoxuridine and to reduce HSE mortality to 54%, with 86% of survivors suffering neurologic impairment. Acyclovir dosed at 30mg/kg/day given in 3 divided doses was found to further improve upon mortality and morbidity, as evidenced by 28% mortality and 62% of survivors having some form of neurologic debility (Whitley et al., 1986). This clinical trial also showed that patients with HSE who are over 30 years of age or have a lower level of consciousness (Glasgow Coma Scale of 6 or less) prior to treatment are at greater risk for a poor therapeutic outcome. Acyclovir is currently the standard of care for treatment of HSE.

Limitations of Antiviral Therapy for HSV CNS Infections

Though advancements in antiviral therapy for HSV infections involving the CNS have led to substantially improved outcomes, the mortality and morbidity due to these infections are still unacceptably high. In patients affected by HSV, the best outcomes are seen when appropriate antiviral therapy is given prior to significant viral replication within the CNS or widespread dissemination throughout the body (Whitley et al., 1988). Theoretically, if clinicians are able initiate appropriate therapy earlier, it may be possible to improve current outcomes. Conversely, the failure to initiate therapy prior to viral dissemination and replication is the

most significant limitation of antiviral treatment. One study of neonates with HSV infection reported that there has not been a trend towards earlier treatment. When comparing 2 time periods during the early acyclovir era of neonatal HSV treatment (1981-1988 and 1989-1997), no significant difference was found in the mean time between onset of disease symptoms and initiation of therapy (Kimberlin et al., 2001b). The authors of this study highlight the need for clinicians to have an increased awareness of HSV infections in an effort to decrease the time to diagnostic evaluation and treatment. It must be noted, however, that duration of neonatal illness prior to initiation of antiviral therapy has not been demonstrated to correlate with neurologic outcome, illustrating the complexity of events occurring in affected babies. Further investigations are required to better delineate the many factors that lead to this complex clinical picture, such as CNS penetration of antiviral agents, deleterious host inflammatory response, differing sites of viral replication, and genetic determinants.

Another limitation to the treatment of HSV CNS infections is the ability to diagnose the infection promptly. Though characteristic findings on magnetic resonance imaging (MRI) of the brain or electroencephalography (EEG) may be helpful, the current gold standard for diagnosis of HSV infection with CNS involvement is the detection of HSV DNA in the CSF by polymerase chain reaction (PCR). Other causes of encephalitis can mimic the MRI findings of HSV CNS infections (Whitley et al., 1989), and though the EEG findings of affected patients often have the classic periodic spike and slow-wave patterns early in the course of disease, this in nonspecific (Mizrahi and Tharp, 1982; Sainio et al., 1983). HSV PCR is more specific and should be able to provide rapid diagnosis; however, some laboratories are unable to perform the test in a timely fashion, and so prompt diagnosis remains a limitation to optimal therapy in many cases. It should also be recognized that negative CSF HSV PCRs have been documented early in the course of illness in cases later confirmed to be HSV infection (Fonseca-Aten et al., 2005). As a consequence, clinical suspicion should always rule when determining management plans.

Determination of the most appropriate duration of antiviral therapy for HSV infections involving the CNS is another potential limitation of therapy. The current course of 21 days is based primarily on the observation that neonates whose CSF remained PCR positive for HSV DNA after completion of 10 days of acyclovir were found to have significant morbidity and mortality (Kimberlin et al., 1996). Because of this, a longer duration of therapy was recommended. Now, with some reports of persistently positive PCR samples after 21 days of acyclovir, some consideration must be given to lengthening the duration of therapy beyond 21 days in certain cases.

Resistance of HSV to antiviral agents has not been a major limitation of therapy to date. Though reported in the laboratory, HSV resistance to acyclovir has not been a clinically important finding in immunocompetent patients, having a reported prevalence of less than 1% (Christophers et al., 1998). In immunocompromised patients, however, clinical strains of acyclovir-resistant HSV have been reported as 6% (Stranska et al., 2005), with higher degree of immunosuppression and more prolonged exposure to the agent being the most significant risk factors for the development of resistance. The most common cause of acyclovir resistance in clinical HSV strains is the deficiency or alteration of the viral thymidine kinase such that acyclovir cannot undergo the initial phosphorylation required for its activity (Gilbert et al., 2002). As acyclovir use for the treatment and suppression of HSV infections increases, further surveys will be necessary to monitor for increases in clinical acyclovir resistance.

CYTOMEGALOVIRUS

CMV is a member of the beta herpesvirus subfamily. It has a linear, double-stranded DNA genome of approximately 229 kbp and is the largest member of the herpesvirus family. The

CMV genome is divided into 2 regions, unique short (US) and unique long (UL), which are used to denote the map positions from which proteins are encoded. For example, the CMV DNA polymerase pUL54 is the protein encoded by the 54th open reading frame of the unique long region.

CMV commonly infects humans worldwide, with a seroprevalence of approximately 40% in adolescents and approaching 90% in adults with low socioeconomic status (Griffiths and Emery, 2002; Staras et al., 2006). Congenital CMV infection is the most common congenital infection in the developed world, found in about 1% of liveborn infants in the United States (Demmler, 1991). Congenital CMV infections most commonly occur via intrauterine transmission, but since the virus is shed in bodily fluids, transmission can also be acquired perinatally during delivery or postnatally through breast milk.

Of all infants born with congenital CMV infection, approximately 7-10% have clinically evident disease at birth (Conboy et al., 1987). Clinical characteristics of intrauterine infection include intrauterine growth restriction, hepatosplenomegaly, jaundice, thrombocytopenia, microcephaly, periventricular calcifications, and chorioretinitis. Approximately two-thirds of infants with symptomatic congenital CMV infection have some form of CNS involvement (Istas et al., 1995). As reviewed by Dollard, true mortality rates are difficult to obtain and have been reported to be as high as 30% for symptomatic infants (Dollard et al., 2007), but more likely average about 5-10% (Ross and Boppana, 2005). Death is usually due to non-CNS manifestations of the infection, such as hepatic dysfunction or bleeding. An estimated 40-58% of infants with symptomatic congenital CMV infection have permanent sequelae, while nearly 14% of infants who are asymptomatic at birth suffer permanent sequelae (Dollard et al., 2007). Sensorineural hearing loss (SNHL), mental retardation, seizures, psychomotor and speech delays, learning disabilities, chorioretinitis, optic nerve atrophy, and defects in dentition are the most common long-term consequences (Griffiths and McLaughlin, 2004). As opposed to intrauterine infections, perinatally acquired CMV infections are not typically associated with long-term sequelae, though acute illness such as hepatitis, thrombocytopenia, and a sepsis-like syndrome has been reported in premature very low birth weight infants (Maschmann et al., 2001). In full term infants, perinatal infections are commonly asymptomatic(Granstrom and Leinikki, 1978), but infants may present with pneumonitis within the first few months of life (Brasfield et al., 1987).

Congenital CMV infection is the consequence of maternal-fetal infection, with most symptomatic congenital cases occurring because of asymptomatic maternal infection. The pathogenesis of CNS involvement in congenital CMV infection begins with disseminated viremic spread, including the endothelial cells of the brain and epithelial cells of the choroid plexus. From the endothelial cells of the brain, the virus spreads to contiguous astrocytes. From the choroid plexus, the virus spreads to the ependymal surfaces via the cerebrospinal fluid (CSF). Once these cells are infected, the virus undergoes continuous replication which leads to characteristic intranuclear inclusion bodies and cell death. As antibodies are produced in the face of continuous viral replication, immune complexes form as well, leading to further immune-mediated damage (Griffiths and McLaughlin, 2004). Although the specific pathogenesis of CMV mediated SNHL has not been elucidated, histology has shown evidence of infection in the cells of both the cochlear and vestibular endolabyrinth (Strauss, 1990). CMV has also been isolated from the cochlear perilymph upon autopsy of infants with congenital CMV infection (Davis et al., 1981). These topics are the subject of a recent review by Cheeran et al (Cheeran et al., 2009).

Initial investigations into potential treatment options for congenital CMV infections have centered on the antiviral agent ganciclovir. Ganciclovir is an acyclic deoxyguanosine nucleoside analog, and has a mechanism similar to acyclovir in that it must undergo

phosphorylation prior to eliciting antiviral activity. The initial phosphorylation step is carried out by pUL97, which is a viral protein kinase. Cellular kinases then phosphorylate the agent 2 additional times to convert it into its triphosphate derivative, which is able to inhibit the CMV DNA polymerase encoded by *UL54* as well as incorporate into and terminate viral DNA. Because ganciclovir has poor oral bioavailability, its prodrug, valganciclovir, was synthesized and has been licensed to treat CMV retinitis in HIV infected individuals as well as CMV disease in some transplant populations. Ganciclovir is also approved for use in immunocompromised patients with systemic CMV infection, along with cidofovir and foscarnet, both of which also inhibit CMV DNA polymerase. Cidofovir undergoes phosphorylation by cellular kinases prior to its inhibition of DNA polymerase, but it does not require the initial step of phosphorylation by a virally encoded enzyme. Foscarnet requires no phosphorylation and instead interacts directly with DNA polymerase.

Recent studies of ganciclovir treatment of congenital CMV infections involving the CNS have been promising. Using intravenous ganciclovir at doses of 12mg/kg/day divided every 12 hours for a duration of 6 weeks, Kimberlin et al demonstrated improved hearing outcomes in neonates with symptomatic congenital CMV infections involving the CNS (as evidenced by microcephaly, intracranial calcifications, abnormal CSF for age, chorioretinitis, and/or hearing deficits) (Kimberlin et al., 2003). The primary endpoint was improved brainstem-evoked response (BSER) between baseline and 6 month follow-up (or no deterioration at the 6 month follow-up if the baseline BSER was normal). For total evaluable ears, 69% of patients who received ganciclovir met the primary endpoint as opposed to 39% of the control group. No patients receiving ganciclovir had worsening of their hearing between baseline and 6 months. Ganciclovir recipients also had more rapid resolution of ALT abnormalities than did the control group, though they were significantly more likely to become neutropenic. Additional analyses of this randomized controlled trial suggest that ganciclovir may also reduce neurodevelopmental delays (Oliver et al., 2006). Improvement of mortality has not yet been shown with ganciclovir therapy.

Limitations of Antiviral Therapy for Congenital CMV Infections

The major limitation of antiviral therapy for congenital CMV infection is the fact that much of the CNS damage occurs *in utero*, prior to our ability to recognize and treat the disease. This highlights the idea that prevention of congenital CMV infection via maternal active immunization may offer the best solution. The results of a recent phase 2 clinical trial showed that recipients of a recombinant CMV envelope glycoprotein B vaccine were significantly less likely to become infected with CMV during the time interval studied when compared to the placebo group (Pass et al., 2009).

While studies of CMV vaccines continue, antiviral therapy for infants with symptomatic congenital CMV infection remains the mainstay. Though recent trials evaluating ganciclovir treatment of congenital CMV infections involving the CNS have had promising results, therapy is not without drawbacks. Potential toxicities such as neutropenia and nephrotoxicity must be considered, as well as the risk of complications in maintaining intravenous access for 6 weeks. In addition, ganciclovir is mutagenic, teratogenic, and carcinogenic in animal models, suggesting that it is prudent to monitor exposed babies for long term adverse events.

The difficulty in correctly identifying all patients who might benefit from antiviral therapy is another limitation. The controlled trial evaluating the effect of ganciclovir on hearing outcomes involved neonates with congenital CMV infection and clinical evidence of CNS disease, but congenital CMV infections in asymptomatic infants can also cause permanent neurologic sequelae (Dahle et al., 2000). It is not yet clear if universal screening for congenital CMV infection would be able to identify these infants or if ganciclovir therapy would be beneficial

for them. At this time, ganciclovir should not be given to infants with asymptomatic congenital CMV infections.

The optimal duration of antiviral therapy for symptomatic congenital CMV disease has not yet been defined. Improved hearing outcomes were shown with a 6 week course of ganciclovir, but it is possible that a longer duration of therapy could be more effective in the prevention of long term sequelae. The observation that a longer duration of therapy leads to improved neurologic outcomes in patients with congenital toxoplasmosis, another infection in which long-standing *in utero* infection leads to long term sequelae (Roizen et al., 1995), lends credibility to this theory. A clinical trial evaluating 6 weeks versus 6 months of therapy with the oral prodrug of ganciclovir, valganciclovir, is currently being conducted by the NIH National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group (CASG 112) (www.casg.uab.edu).

Another limitation of antiviral therapy for congenital CMV infection is the persistence of viral replication within the cochlear perilymph. Though it had previously been shown that CMV can be isolated from the perilymph of affected infants (Davis et al., 1981), more recent studies utilizing PCR have shown evidence of ongoing viral replication within the perilymph in children up to 4 years of age (Bauer et al., 2005; Sugiura et al., 2004). Since these patients had not been previously treated, it is not certain that this persistence of CMV within the perilymph also occurs in infants who receive ganciclovir. In a guinea pig model, ganciclovir obtained higher levels in perilymph than in CSF, indicating that the agent should be able to exert its antiviral activity in this compartment (Woolf et al., 1988). However, a previous report that there is no significant difference in the duration of urinary excretion of CMV between treated and untreated patients with congenital CMV infection (Noyola et al., 2000) suggests that it is at least possible for persistence of viral replication to occur regardless of treatment. This may indicate that SNHL is an ongoing process over the first several years of life rather than a single hit early in infancy. In the face of an ongoing viral process such as this, a one-time, relatively short course of therapy may not be the optimal treatment duration.

The development of resistance to antiviral agents has become a limiting factor in the treatment of CMV infections in general, though less so for congenital CMV infections thus far. As reviewed by Gilbert and Boivin, drug-resistant strains of CMV are an emerging problem for immunocompromised patients, such as transplant recipients (including solid organ, bone marrow, and hematopoietic stem cell transplants) and AIDS patients (Gilbert and Boivin, 2005). Mutations within the *UL97* and *UL54* genes are the most common causes of CMV antiviral resistance, with *UL97* mutations having the potential to confer resistance to ganciclovir and *UL54* mutations having the potential to confer resistance to ganciclovir, cidofovir, or foscarnet. A temporal association has been established between length of antiviral therapy and the emergence of resistant CMV strains. With ganciclovir, for instance, one study evaluating AIDS patients with CMV retinitis showed that 2.7% of patients had a ganciclovir-resistant CMV strain at the time of diagnosis, compared to 11.4% and 27.5% after 6 months and 9 months of ganciclovir therapy, respectively (Jabs et al., 1998). As investigations into the possible benefits of longer treatment courses for congenital CMV infections progress, this association between increased duration of therapy and the emergence of ganciclovir-resistant CMV strains will need to be monitored.

FUTURE NEEDS

Further advancements in the treatment of herpesvirus CNS infections are needed to improve outcomes even more. Two particular areas in need of improvement were mentioned previously — earlier initiation of therapy for HSV CNS infections, and determination of optimal treatment duration for congenital CMV infections. As shown in patients with neonatal HSV infections,

the availability of an effective antiviral agent has not led to a trend towards earlier diagnosis (Kimberlin et al., 2001b). Improvements in diagnostic capabilities, such as the availability of PCR, have been helpful in this effort, but clinicians must still have a low threshold when evaluating patients with possible HSV CNS infections. Concerning congenital CMV infections involving the CNS, the primary need at this time is the determination of whether or not a longer treatment course could further improve upon hearing and neurodevelopmental outcomes. The previously mentioned CASG clinical trial evaluating 6 weeks versus 6 months of valganciclovir is in progress, utilizing a valganciclovir dose determined in phase I/II study to produce equivalent ganciclovir blood concentrations as does intravenous ganciclovir (Kimberlin et al., 2008).

Novel antiviral agents effective against herpesviruses are an active area of research. The primase-helicase inhibitors, for example, are a new class of agents that prevent replication of HSV. The most promising member of this class, BAY 57-1293, has been shown to have superior *in vitro* activity when compared to other antiviral agents currently used to treat HSV infections (Betz et al., 2002). Due to the toxicity limitations and increasing resistance patterns of ganciclovir, the development of new compounds active against CMV is particularly important. Several anti-CMV agents are in development, the most promising of which are reviewed here.

Maribavir (GW1263W94) is a benzimidazole L-riboside whose mechanism of activity has been mapped to the viral protein products of *UL97* and *UL27* (Biron et al., 2002; Komazin et al., 2003). Although some degree of inhibition of DNA synthesis is apparent, maribavir's primary mode of action is thought to be inhibition of nuclear egress of newly-formed viral capsids (Krosky et al., 2003). Because one of maribavir's targets, pUL97, is necessary for ganciclovir's antiviral activity, there is a concern that the two agents could be antagonistic when used together. Despite previous reports to the contrary (Evers et al., 2002; Selleseth et al., 2003), a recent study has described the presence of this antagonism between maribavir and ganciclovir (Chou and Marousek, 2006). There does not appear to be any cross-resistance between maribavir and ganciclovir due to mutations within *UL97* (Schleiss and McVoy, 2004). Unfortunately, with maribavir's recent failure in a phase 3 trial of a hematopoietic stem cell transplant population, it is unlikely that it will be investigated as a potential congenital CMV infection therapy.

Other antiviral agents with activity towards CMV that are in development or in clinical trials include GW275175X, tomeglovir (BAY 38-4766), hexadecyloxypropyl-cidofovir (HDP-CDV), and octadecyloxyethyl-cidofovir (ODE-CDV). GW275175X is a derivative of the halogenated benzimidazole family and is an analogue of maribavir. Its mechanism of action involves prevention of viral DNA maturation during the replicative process by inhibition of viral DNA cleavage and packaging into capsids (Underwood et al., 2004). Tomeglovir is a non-nucleoside inhibitor of CMV that acts in a manner similar to the benzimidazoles in that it affects the late stages of viral replication — DNA cleavage and packaging (Buerger et al., 2001). HDP-CDV and ODE-CDV are lipophilic prodrug derivatives of cidofovir that offer increased bioavailability and decreased nephrotoxicity, but also appear to have enhanced antiviral activity against CMV when compared to their parent drug (Beadle et al., 2002).

Essential to the development of any new therapeutic aimed at herpesvirus CNS infections is the lipophilicity of the agent(s). Even with excellent antiherpetic medications, such as acyclovir, penetration into the infected brain tissue is both slow and incomplete. Among patients who have died from HSE, it is possible to recover logs of virus from brain tissue at autopsy. Highly lipophilic agents are able to penetrate more thoroughly into affected brain tissue (Ciesla et al., 2003).

Along with the development of new antiviral agents, adjuvant and combination therapies are also being investigated in an effort to maximize the efficacy of treatment of herpesvirus CNS infections. Similar to the HIV model of antiviral therapy, combination therapy with agents of differing mechanisms of activity may yield enhanced antiviral effects. Though no clinical data yet exists, established and novel anti-CMV agents are being evaluated for possible antagonistic or synergistic effects (Evers et al., 2002; Selleseth et al., 2003).

Adjuvant therapies for HSE are also under investigation. In a retrospective analysis of adults with HSE who were treated with acyclovir, Kamei et al determined that corticosteroid administration was an independent predictor of better outcome, along with lower age and higher initial level of consciousness (Kamei et al., 2005). A recent study has also shown a possible neuroprotective effect of delayed glucocorticoid administration in a mouse model of HSE (Sergerie et al., 2007). When compared to those that received no glucocorticoid or glucocorticoid concomitant with their infection, mice that were given a glucocorticoid 72 hours after infection showed less neuronal damage, reduced expression of viral thymidine kinase and DNA polymerase genes, and higher life expectancy. Further studies are needed to determine if there is indeed a benefit to critically timed glucocorticoid administration as an adjuvant to acyclovir.

Type I and II interferons, which have endogenous antiviral activity, are also being considered for adjuvant therapy (Peng et al., 2008; Taylor et al., 1998). However, one controlled clinical trial evaluating acyclovir plus recombinant interferon-beta in children showed no significant difference in outcomes when compared to acyclovir plus placebo (Wintergerst et al., 2005). Cytokine modulation in an effort to reduce neuronal damage secondary to host inflammatory response is another avenue that has been proposed for HSE. Further studies are needed to develop and evaluate agents that can act to down-regulate the host inflammatory response.

CONCLUSIONS

The ideal method of prevention of CMV and HSV CNS infections clearly is active immunization. While vaccines are under investigation for both infections, vaccine efficacy protecting the CNS may prove to be difficult. Meanwhile, advances in antiviral therapies available for treatment of CNS infections due to herpesviruses have led to significant improvement in the morbidity and mortality associated with these diseases. Despite this fact, limitations to optimal outcomes still exist with the challenges of appropriate early initiation of therapy, drug toxicities, and developing resistance. Recent and forthcoming advances in diagnostic capabilities, novel antiviral agents, and adjuvant and combination therapies will help clinicians to achieve the best possible outcomes, but the need for increased clinical awareness of herpesvirus CNS infections will remain vital to the correct diagnosis and treatment of these diseases.

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