Available online at www.sciencedirect.com
ScienceDirect
Antiviral Research 71 (2006) 164–171
Antiviral Research
www.elsevier.com/locate/antiviral

Mini-review

Pivotal role of animal models in the development of new therapies for cytomegalovirus infections

Earl R. Kern *

The University of Alabama at Birmingham, Department of Pediatrics, CHB 128, 1600 6th Avenue South, Birmingham, AL 35233, United States

Received 24 April 2006; accepted 30 May 2006

Dedicated to Professor Erik De Clercq on the occasion of reaching the status of Emeritus Professor at The Katholieke Universiteit Leuven, Belgium.

Abstract

Since human cytomegalovirus (CMV) is extremely species specific and does not replicate in experimental animal tissues, animal models for the evaluation of antiviral agents for these infections have utilized surrogate animal viruses including murine CMV, rat CMV and guinea pig CMV. Murine CMV and rat CMV infections in normal and immunocompromised animals provide models of disseminated infection and are ideal for screening of new agents. While guinea pig CMV infection in immunocompromised animals also provides a model for disseminated disease, the model for congenital CMV is unique among all the experimental models. While these models have played a major role in the development of ganciclovir, foscarnet and cidofovir, they do not provide information directly related to human CMV, nor are they useful for evaluation of agents that are active only against human CMV. The SCID-hu mouse models in which human tissue is infected with human CMV has been very useful in the development of new antiviral agents such as maribavir and cyclopropavir. Collectively these experimental CMV infections provide a variety of models representing various aspects of CMV infection in humans that are highly predictive for antiviral efficacy in humans.

Keywords: Cytomegalovirus; Animal models; Mouse; Rat; Guinea pig

Contents

1. Introduction to human cytomegalovirus infections

The results from several studies have indicated that congenital cytomegalovirus (CMV) infection occurs at a frequency of about 1–2% of all live births (Alford, 1984; Nelson and Demmler, 1997) and results in a significant amount of damage to the CNS including hearing loss and mental retardation (Reynolds et al., 1974; Kimberlin et al., 2003; Fowler and Boppana, 2006; Boppana et al., 2005). CMV infections continue to be a problem in the immunocompromised host (de Jong et al., 1998) and although significant advances have been made in the treatment of HIV-infected patients and the incidence of CMV in these patients

* Tel.: +1 205 934 1990; fax: +1 205 975 1992.
E-mail address: Kern@uab.edu.

0166-3542/$ – see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.antiviral.2006.05.018

has decreased substantially (Reed et al., 1997; Palella et al., 1998; Tural et al., 1998; O'Sullivan et al., 1999), there is ongoing concern that due to drug resistance, the incidence of retinitis and other CMV infections may be on the rise (Bowen et al., 1998; Jabs et al., 1998, 2005). CMV infections also continue to be a major cause of morbidity in patients immunosuppressed as a result of solid organ or stem cell transplantation (Crippa et al., 2001; Enright et al., 1993; Ljungman, 2002; Meyers et al., 1986; Razonable and Paya, 2003). The treatment of choice for these infections has primarily been intravenous ganciclovir (GCV) (Goodrich et al., 1993; Winston et al., 1988, 1993; Kimberlin et al., 2003); however, its use for long-term maintenance therapy for persistent CMV infections has been problematic due to the development of toxic side effects such as neutropenia and the development of resistant isolates (Boivin et al., 2001; Chou et al., 2003; Erice et al., 1998; Limaye et al., 2000, 2002). Other therapies have included acyclovir (ACV), particularly for long-term prophylaxis (Balfour et al., 1989) or foscarnet (PFA) for GCV-resistant CMV. The advent of orally active valacyclovir and valganciclovir have facilitated the delivery of ACV and GCV (Balfour et al., 1989; Lowance et al., 1999; Paya et al., 2002; Winston et al., 2003) but have not reduced the problem of toxicity or emergence of isolates resistant to GCV (Boivin et al., 2001). Although cidofovir (CDV) and PFA are approved for use in treatment of these infections, both are too toxic for long-term use (Polis et al., 1995; Lalezari and Kuppermann, 1997; Ringden et al., 1986; Safrin et al., 1997; Razonable and Paya, 2003). The ongoing nature of these problems for therapy of CMV infections has continued to underscore the importance of developing additional therapies for these infections, in particular ones that have less toxicity and are active against GCV- and PFA-resistant mutants.

2. Human CMV infections in mice using implanted human tissues

As part of the development of new drugs for CMV infections, there is a need for better animal models that more closely mimic CMV infections in humans (Kern, 1997). Since human CMV does not replicate in non-human tissues, most models have utilized surrogate animal viruses such as murine CMV (MCMV) (Shanley and Pesanti, 1985; Kern, 1991, 1999; Smee et al., 1992, 1994; Kern et al., 2004a,b,c), rat CMV (RCMV) (Stals et al., 1990, 1991, 1993; Stals, 1999) and guinea pig CMV (GPCMV) (Lucia et al., 1984; Li et al., 1990; Bernstein and Bourne, 1999; Bia et al., 1983; Bourne et al., 2000; Bravo et al., 2006). These animal models have made major contributions to the development of GCV, CDV and foscarnet. However, since there are many compounds that are active against human CMV that are not active against any of the animal viruses (Weber et al., 2000; Williams et al., 2003), there is a need for an animal model in which human CMV is replicating in human cells or tissues. There have been only a few novel approaches for developing animal models in which human cells or tissues have been engrafted or implanted in immunocompromised animals and infected with HCMV. These include the use of HCMV-infected fibroblast cells entrapped in agarose plugs (Allen et al., 1992; Weber et al., 2000), human tumor cell lines that are permissive for HCMV replication implanted in nude mice (Pari et al., 1998), the use of human fetal retinal tissue implanted into the anterior chamber of eyes of SCID mice or athymic rats (Epstein et al., 1992; DiLoreto et al., 1994; Laycock et al., 1997; Bidanset et al., 1999) or thymus/liver (thy/liv) tissue implanted under the kidney capsule of SCID mice (Mocarski et al., 1993; Brown et al., 1995; Kemble et al., 1999) and subsequently infected with HCMV. However, there has been only a few cases where these models have been used for the evaluation of new antiviral therapies (Weber et al., 2000; Bidanset et al., 2001, 2004, 1999; Kern et al., 2001, 2004a,b,c).

In our laboratory we have extended the work of DiLoreto et al. (1994) using human retinal tissue implants and that of Mocarski et al. (1993) for thy/liv implants in SCID mice. In both of these model systems we have definitively established the replication kinetics of infectious human CMV in implanted tissue. In order to validate the appropriateness of these two model infections for use in the evaluation of new antiviral therapies for HCMV infections, we have determined the effect of treatment with GCV and CDV (Bidanset et al., 2004; Kern et al., 2001) as these are currently the most commonly used drugs for treatment of CMV infections in humans.

For the ocular model, fetal human retinal tissue was implanted in the anterior chamber of the SCID mouse eye and inoculated 6–9 weeks later with 2000–7500 plaque-forming units (pfu) of HCMV. In the second model, fetal thymus and liver (thy/liv) tissue was implanted under the kidney capsule of SCID mice and inoculated 12–14 weeks later with 2200–9000 pfu of HCMV. At various times after infection, implant tissues were removed, homogenized and HCMV titers quantified by plaque assay. The replication of the Toledo strain of HCMV in both models was similar in that viral titers increased through day 21, remained high through day 35 and then gradually decreased (Kern et al., 2001). To validate the two models, the efficacy of GCV and CDV was determined in both ocular and thy/liv models. In SCID-hu retinal tissue, once daily i.p. treatment with 33 mg GCV per kg significantly reduced viral titers (2–20-fold) between 14 and 28 days after infection. In SCID-hu thy/liv implants, the same treatment regimen reduced viral replication either completely or by 3–5 $\log_{10}$. In retinal implant tissue, i.p. treatment with 25 mg CDV per kg once daily for 14 days, followed by three times weekly for the next 14 days, reduced viral titers by 2–3 $\log_{10}$ between 10 and 42 days after infection. In comparison, once daily i.p. administration of 30 mg CDV per kg completely inhibited HCMV replication in thy/liv implants. The higher levels of efficacy seen in the thy/liv implants compared to the retinal tissue implants is probably due to the ability of the drug to gain access to infected tissue in the kidney versus crossing of the blood–ocular barrier. The results from these studies indicated that both the SCID-hu retinal and SCID-hu thy/liv implant models are useful for determining in vivo activity against HCMV and appear to be predictive of efficacy for both ocular and systemic infections in humans (Kern et al., 2001).

We have also determined the efficacy of a benzimidazole ribonucleoside (1263W94, maribavir [MBV]) in these two models (Kern et al., 2004c). This compound had no activity against

MCMV, RCMV or GPCMV in vitro (Williams et al., 2003). Treatment was initiated 24 h after HCMV infection of the implants and continued for 28 days. Treatment consisted of either placebo, 25 mg of GCV/kg administered i.p. twice daily or 75 mg of MBV/kg administered orally twice daily. GCV was effective in both models, inhibiting HCMV infection by 5–3000-fold. In the retinal tissue model MBV reduced HCMV replication about four-fold through 21 days post-infection compared with results for the vehicle control. In thy/liv implants, MBV was effective in inhibiting HCMV replication by approximately 30–3000-fold in comparison to the vehicle control. These results indicated that MBV was efficacious in these animal models of HCMV and suggest that this class of compounds may be active against the various HCMV infections that occur in the immunocompromised host (Wang et al., 2003).

We reported previously that purine 2-(hydroxymethyl)-methylenecyclopropane analogs have good activity against CMV infections in vitro and in vivo (Rybak et al., 1999, 2000). A second-generation analog (*Z*)-9-{[2,2-bis(hydroxymethyl)cyclopropylidene]methyl}guanine (ZSM-I-62, cyclopropavir [CPV]) has particularly good activity against MCMV and HCMV in vitro (Kushner et al., 2003). To determine the oral activity of this compound against HCMV in vivo, SCID mice were implanted with human fetal retinal or thy/liv tissues. In general, replication of HCMV in both types of implanted tissue increased from 7 through 21–28 days and then gradually decreased to undetectable levels by 8 weeks post-infection. Oral treatment with 45 or 15 mg of CPV/kg initiated 24 h after infection was highly effective in reducing replication to undetectable levels in both models and was generally more effective than GCV (Kern et al., 2004a). These results indicated that the methylenecyclopropane analog, CPV, was highly efficacious in these four animal models and should be evaluated for use in CMV infections in humans.

We have also evaluated two orally active ether lipid ester analogs of CDV, hexadecyloxypropyl-CDV (HDP-CDV) and octadecyloxyethyl-CDV (ODE-CDV) in the two SCID-hu mouse models. The results indicated that orally administered treatment with either HDP-CDV or ODE-CDV was four to eight-fold more active, on a molar basis, than was i.p. administered CDV (Kern et al., 2004b). These results also suggest that HDP-CDV or ODE-CDV should be further evaluated as potential antiviral agents for treatment of HCMV infection. Although the SCID-hu mouse models using HCMV are very labor intensive and expensive, they provide excellent models for evaluation of new antiviral therapies for HCMV infection and are particularly useful when an antiviral agent is not active against murine, rat or guinea pig CMV strains.

3. Murine CMV infection

Inoculation of mice with MCMV provides a model infection that shares many characteristics with the human disease. Both acute lethal and chronic non-lethal MCMV infections have been used in our laboratory to determine efficacy of antivirals (Kern, 1991, 1997, 1999). After i.p. inoculation of 3-week-old Swiss–Webster female mice with 1×10^6 pfu of MCMV, 90–100% of animals die with a mean day of death of 5–6 days; however, if the inoculum is reduced to 1×10^5 pfu, all animals survive. With either inoculum high titers of virus are present in lung, liver, spleen, kidney and blood within 24 h and in the salivary gland by 48–72 h after viral inoculation. In the non-lethal infection, persistent viral replication occurs in lung, liver, kidney and spleen for 45–60 days and in salivary glands for months (Kern, 1999). In Balb/c mice infected with MCMV immunosuppression with cyclophosphamide results in a severe interstitial pneumonitis (Shanley and Pesanti, 1985) and a disseminated infection. The MCMV infection, therefore, involves many of the same target organs as CMV infections in humans and has been shown to be an excellent model for predicting the outcome of therapy in human CMV diseases (Kern, 1991, 1997).

The murine CMV models lend themselves well to the use of i.p., subcutaneous or oral therapy. This model was particularly useful in the preclinical development of both GCV (Smee et al., 1994; Smee et al., 1992; Neyts et al., 1992; Kern, 1991; Duan et al., 1998) and CDV (Kern, 1991, 1999; Neyts et al., 1992). In general, CDV could be administered later in the course of infection and at lower dosages than GCV and still alter mortality. If treatment was delayed for 48 h, the mortality rate for the two drugs was comparable at the highest doses tested but substantially lower for mice given smaller doses of CDV. These latter results were particularly exciting as they indicated that treatment initiated in mice as late as 48 h following exposure to MCMV (especially with CDV) can still have a mortality-sparing effect on the course of disease—a remarkable finding considering that untreated MCMV-infected animals begin to die as early as 3–4 days post-infection. The results also indicated that CDV administered beginning 4 days after MCMV infection and at a time when virus titers are at peak levels can drastically alter replication soon after therapy is initiated (Kern, 1999). In other experiments the chronic infection has been used to investigate the efficacy of twice a week dosing for 60 days, indicating that an MCMV chronic infection is a very sensitive and useful model for determining the effect of maintenance therapy on viral replication in target organs.

Murine CMV infection of SCID mice provides an ideal model for CMV infections in the immunocompromised host (Smee et al., 1992; Neyts et al., 1992; Kern et al., 1999). When this model infection is utilized for evaluation of treatment such as the use of twice weekly CDV for 3 weeks, animals survive on an effective regimen as long as drug is being administered. However, because the animals do not have a normal immune system, the animals cannot clear the virus and all die soon after drug is discontinued and do so in a dose-dependent fashion. These results indicated that inoculation of SCID mice with 1–3 pfu of MCMV results in a disseminated infection with viral replication in the same target organs as seen in immunodeficient patients (Kern, 1999). These animals have high levels of virus in their tissues for at least 2–3 weeks, which should allow adequate time to document an antiviral response in treated animals compared with placebo animals. It is interesting to note that, although SCID mice are more susceptible to infection and death than normal mice, the rate of virus replication in target organs is considerably reduced

compared to normal mice and mortality is delayed by 1–2 weeks (Kern, 1999).

Much of our understanding of the pathogenesis and latency of CMV infections in humans has come from the study of MCMV infections. The murine virus and the animal model closely resemble HCMV and many aspects of CMV infection of humans, so a lot of valuable information obtained in the animal can be extended to human disease. Since there are only three antiviral drugs approved for treatment of CMV infection in humans, there is not a lot of information available to establish the predictability of the experimental infections. All three of these drugs, GCV, PFA and CDV, were shown to be very effective in the MCMV infection and these models played a major role in the pre-clinical development of these therapies (Kern, 1991, 1997, 1999). Murine CMV infection in normal or immunocompromised mice have also been used to determine the potential of a number of new antiviral agents. These include a novel peptide aldehyde (Weber et al., 2000), methylenecyclopropane analogs (Rybak et al., 1999; Kern et al., 2004a), the benzimidazole ribonucleosides (Kern et al., 2004c) and lipid ether esters of CDV (Kern et al., 2004b). A number of these new compounds that showed excellent activity in the murine model are either in clinical studies or hopefully will begin in the near future.

4. Rat CMV infection

Infection of immunocompentent rats with RCMV results in an asymptomatic infection, whereas under immunocompromised conditions a generalized disseminated infection develops (Stals et al., 1990; Stals, 1999). The effect of a number of antiviral agents have been evaluated in the RCMV model including GCV (Stals et al., 1991, 1993), PFA (Stals et al., 1991), CDV (Stals et al., 1991, 1993) and ACV (Bruggeman et al., 1987). Studies on the effect of GCV treatment indicated that the drug was effective against generalized RCMV infection in a dose-dependent manner (Stals et al., 1991). The effective dose was 20 mg/kg per day given in two daily doses for 5 days. Shortening the duration of treatment and delaying treatment for 3 days led to therapy failure and all animals died from infection. In this model CDV was far more active than GCV in that dosages that were 10-fold less provided protection against mortality. One single dose of CDV at 20 mg/kg completely inhibited viral replication in all organs. Neither drug was efficacious if treatment was delayed until 3 days after infection. Prophylactic administration with CDV, but not GCV, was effective in reducing mortality from generalized infection. Similar results were observed using another model for immunosuppressed patients, allogeneic BMT in rats (Stals et al., 1993). The results obtained in the RCMV models further supported the efficacy of GCV and CDV that was observed in the MCMV models for treatment of HCMV infection. The results from the rat CMV model are in close agreement with those obtained in the murine models, but their size and costs are disadvantages to the model.

A major role for the RCMV model may be for investigation of CMV-mediated development of vascular disease particularly in atherosclerosis, arterial restenosis and transplant vascular sclerosis (Kaptein et al., 2006). The use of this model may help provide new information on CMV targets for development of new antiviral therapies for certain vascular diseases.

5. Guinea pig CMV infection

The guinea pig models of CMV have been developed to mimic the clinical manifestations of the disease in humans. Two basic models have been utilized to study the pathogenesis of GPCMV disease and to examine the effects of antiviral agents. In one model pregnant dams are infected with GPCMV resulting in infection and frequently death of the fetus. In the other immunocompromised animals are infected with GPCMV leading to the death of the animal. The biology of GPCMV infection in these two models has been reviewed in detail by Bernstein and Bourne (1999) and Schleiss and Lacayo (2006).

5.1. Congenital and neonatal models

The guinea pig is the only small animal model of CMV in which virus crosses the placenta to infect and damage the fetus. Primary infection of pregnant animals results in a vertical transmission rate of 40–80%, similar to the infection rate in humans (Bernstein and Bourne, 1999). The highest vertical transmission rates and highest newborn mortality occur with GPCMV inoculation during late gestation and infection in early pregnancy or just prior to conception is associated with a high rate of fetal resorptions (Harrison and Myers, 1990). If high-enough titers of a virulent salivary gland virus are used, most pregnant dams will not survive to delivery of their pups (Griffith et al., 1990). The duration and titer of GPCMV in the blood and selected organs including the lungs, spleen, kidney and salivary gland can be followed (Griffith et al., 1982) and the impact of treatment evaluated. Virus can also be isolated from the placentas of infected animals (Choi and Hsiung, 1978). Mortality and infection of the offspring are the most common end-points for evaluation of interventional strategies. Virus can be isolated from pups at about 1 week after maternal inoculation and frequently persist through the newborn period. Virus is most often recovered from the spleen and salivary gland but can also be recovered from the blood, liver, lungs, kidneys and brain of infected newborns (Harrison and Myers, 1990).

Since congenitally infected guinea pigs generally die prior to or shortly after birth, newborn animals have been infected with GPCMV within a few days of birth to provide a model for evaluating an antiviral drug in newborn infants congenitally infected with CMV (Bravo et al., 2003). After i.p., inoculation of 10^6 pfu of GPCMV, there was a rapid dissemination of virus to liver and spleen. Virus replication was also detected at later time points in lung and brain. The model, therefore, has many similarities to disseminated CMV infection in human infants including pneumonitis, hepatitis and infection of the CNS. The only compound tested in the neonatal model has been cyclic CDV. Treatment with 5 mg/kg of drug once daily for 7 days, i.p. beginning 24 h after virus inoculation resulted in reduced virus replication in the liver and spleen and a significant reduction in mortality (Bravo et al., 2003).

There have been two published studies using the congenital GPCMV model for evaluation of an antiviral drug. In the experiments by Bravo et al. (2006), treatment of GPCMV-infected pregnant guinea pigs with a single dose (35 mg/kg) of cyclic CDV (HPMPC) improved the outcome of congenital infection by allowing the continuation of pregnancy and increasing the survival of pups. Treatment also significantly decreased viral load detected in the tissues of treated guinea pigs including the placenta. However, at the dose regimen used, cyclic CDV did not prevent the infection of fetuses. In contrast, however, Schleiss et al. (2006) reported that treatment with cyclic CDV could prevent infection of the fetus. Of interest is the fact that passively administered antibody was also effective in the congenital model of GPCMV (Bratcher et al., 1995) and may have a role in treatment of congenital infections in humans (Nigro et al., 2005).

Another very important disease caused by congenital CMV infection that is also manifested in the guinea pig model is labyrinthitis and sensorineural hearing loss (Woolf et al., 1989). In one study prophylaxis with GCV prevented the development of cochlear histopathologic changes and hearing loss (Woolf et al., 1988). The use of hearing loss as an end-point for determining efficacy of antiviral therapy further strengthens the guinea pig as a model for congenital CMV infection.

5.2. *Immunocompromised model*

After GPCMV inoculation, adult immunocompetent outbred Hartley guinea pigs experience transient splenomegaly, a self-limited viremia and peripheral blood mononucleosis similar to that observed in humans (Griffith et al., 1981; Bia et al., 1983). A number of investigators have used immunosuppressive agents in attempts to increase the severity of CMV infection in guinea pigs which would more closely mimick the clinical disease in HCMV infections (Bernstein and Bourne, 1999). The principal clinical endpoint used in immunocompromised animals is mortality and mean day of death. Blood samples can be obtained at various times to measure the magnitude and duration of viremia. Viral quantification in visceral organs (liver, lung, spleen and salivary gland) can also be used to evaluate the efficacy of therapy.

The guinea pig model of CMV infection in immunocompromised animals has been used to evaluate a number of antiviral therapies (Lucia et al., 1984; Fong et al., 1987; Yang et al., 1989; Li et al., 1990). The efficacy of GCV treatment has been examined in both immune competent and immunocompromised animals (Fong et al., 1987) where it provided only a modest antiviral effect. However, in vitro, GPCMV is less susceptible to GCV than HCMV, so decreased efficacy might have been predicted. The guinea pig model has also been useful in predicting the toxicity of certain antiviral compounds. Thus, while CDV had similar activity against both human CMV and GPCMV in vitro, evaluation in vivo revealed significant renal toxicity in guinea pigs (Li et al., 1990; Bravo et al., 1993). Renal toxicity due to CDV was later identified as a significant problem in patients. The cyclic derivative of CDV, however, has reduced toxicity in guinea pigs and has been evaluated in a GPCMV infection in immunocompromised animals (Bourne et al., 2000). Guinea pigs were treated either once daily for 7 days with 5 mg/kg per day or received two doses of 17.5 mg/kg administered on days 1 and 4 post-inoculation and each of the two regimens provided significant protection against mortality. The effect of cyclic CDV treatment on virus replication in liver, lung and spleen was also determined. On day 7 post-inoculation the incidence of virus recovery from the spleen was significantly reduced but only marginally reduced in the liver of treated animals. There was no reduction in the incidence of virus recovery from lungs. By day 10 post-inoculation, treatment did not significantly reduce the incidence of virus isolation from any of the three tissues. The GPCMV infection in immunocompromised guinea pigs was also used to evaluate a new non-nucleoside antiviral, Bay 38-4766 (Schleiss et al., 2005). In their studies, oral treatment with 50 mg/kg drug reduced mortality as well as viremia and DNAemia.

The guinea pig models for CMV are also cumbersome and expensive and do not lend themselves for screening of antiviral agents as well as murine CMV does. They appear to be excellent models however, for determining the effect of therapy on disseminated and congenital infections.

6. CMV infection in non-human primates

Cytomegaloviruses have been isolated and characterized from a number of primate species including chimpanzees, baboons, rhesus macques and other monkeys (Britt, 2006). Although the viruses from these non-human primates may share similarities in their genomic structure to human CMV, and may closely resemble human CMV infections, particularly congenital infections (Barry et al., 2006), it is not likely that these animals will be utilized as models for evaluation of new antiviral agents due to the high costs for purchase and maintenance as well as their lack of availability of sufficient numbers.

7. Summary and conclusion

Animal models have played a pivotal role in the development of antiviral agents for HCMV infections in the past and will certainly continue to do so for newer therapies. The murine model should continue to be the model of choice for in vivo screening of new agents due to their small size, high availability and low cost. The rat model does not appear to add any real advantages over the mouse and is a disadvantage for the reasons of cost and size. The guinea pig model in immunocompromised animals provides a disseminated infection similar to that seen in immunosuppressed mice inoculated with MCMV but may be at a disadvantage because of the significant increase in the cost of guinea pigs. Of great importance, however, is the guinea pig model of congenital CMV which has no other counterpart in the rodent models. Although the SCID-hu mouse models inoculated with human CMV are very labor intensive and costly, they provide excellent models for compounds that are not active against the animal CMV strains. Additionally, they provide information on the effect of therapy in some of the same target tissues as seen in CMV infections in humans. The use of non-human primates for evaluation of antiviral therapies does not appear to be a viable option.

References

Alford, C.A., 1984. Chronic intrauterine and perinatal infections. In: Galasso, G.J., Merigan, T.C., Buchanan, R.A. (Eds.), Antiviral Agents and Viral Diseases of Man. Raven Press, New York, pp. 443–486.

Allen, L.B., Li, S.X., Arnett, G., Toyer, B., Shannon, W.M., Hollingshead, M.G., 1992. Novel method for evaluating antiviral drugs against human cytomegalovirus in mice. Antimicrob. Agents Chemother. 36, 206–208.

Balfour Jr., H.H., Chace, B.A., Stapleton, J.T., Simmons, R.L., Fryd, D.S., 1989. A randomized, placebo-controlled trial of oral acyclovir for the prevention of cytomegalovirus disease in recipients of renal allografts. N. Engl. J. Med. 320, 1381–1387.

Barry, P.A., Lockridge, K.M., Salamat, S., Tinling, S.P., Yue, Y., Zhou, S.S., Gospe Jr., S.M., Britt, W.J., Tarantal, A.F., 2006. Non human primate models of intrauterine cytomegalovirus infection. ILAR J. 47, 49–64.

Bernstein, D.I., Bourne, N., 1999. Animal models for cytomegalovirus infections: guinea-pig CMV. In: Zak, O., Sande, M.A. (Eds.), Handbook of Animal Models of Infection. Academic Press, San Diego, pp. 935–941.

Bia, F.J., Griffith, B.P., Fong, C.K., Hsiung, G.D., 1983. Cytomegaloviral infections in the guinea pig: experimental models for human disease. Rev. Infect. Dis. 5, 177–195.

Bidanset, D.J., Beadle, J.R., Wan, W.B., Hostetler, K.Y., Kern, E.R., 2004. Oral activity of ether lipid ester prodrugs of cidofovir against experimental human cytomegalovirus infection. J. Infect. Dis. 190, 499–503.

Bidanset, D.J., del Cerro, M., Lazar, E.S., Faye-Petersen, O., Kern, E.R., 1999. Animal model for ocular human cytomegalovirus infections in SCID-hu mice. In: Zak, O., Sande, M.A. (Eds.), Handbook of Animal Models of Infection. Academic Press, London, United Kingdom, pp. 957–962.

Bidanset, D.J., Rybak, R.J., Hartline, C.B., Kern, E.R., 2001. Replication of human cytomegalovirus in severe combined immunodeficient mice implanted with human retinal tissue. J. Infect. Dis. 184, 192–195.

Boivin, G., Gilbert, C., Gaudreau, A., Greenfield, I., Sudlow, R., Roberts, N.A., 2001. Rate of emergence of cytomegalovirus (CMV) mutations in leukocytes of patients with acquired immunodeficiency syndrome who are receiving valganciclovir as induction and maintenance therapy for CMV retinitis. J. Infect. Dis. 184, 1598–1602.

Boppana, S.B., Fowler, K.B., Pass, R.F., Rivera, L.B., Bradford, R.D., Lakeman, F.D., Britt, W.J., 2005. Congenital cytomegalovirus infection: association between virus burden in infancy and hearing loss. J. Pediatr. 146, 817–823.

Bourne, N., Bravo, F.J., Bernstein, D.I., 2000. Cyclic HPMPC is safe and effective against systemic guinea pig cytomegalovirus infection in immune compromised animals. Antiviral Res. 47, 103–109.

Bowen, E.F., Emery, V.C., Wilson, P., Johnson, M.A., Davey, C.C., Sabin, C.A., Farmer, D., Griffiths, P.D., 1998. Cytomegalovirus polymerase chain reaction viraemia in patients receiving ganciclovir maintenance therapy for retinitis. AIDS 12, 605–611.

Bratcher, D.F., Bourne, N., Bravo, F.J., Schleiss, M.R., Slaoui, M., Meyers, M.G., Bernstein, D.I., 1995. Effect of passive antibody on congenital cytomegalovirus infection in guinea pigs. J. Infect. Dis. 172, 944–950.

Bravo, F.J., Bourne, N., Schleiss, M.R., Bernstein, D.I., 2003. An animal model of neonatal cytomegalovirus infection. Antiviral Res. 60, 41–49.

Bravo, F.J., Cardin, R.D., Bernstein, D.I., 2006. Effect of maternal treatment with cyclic HPMPC in the guinea pig model of congenital cytomegalovirus infection. J. Infect. Dis. 193, 591–597.

Bravo, F.J., Stanberry, L.R., Kier, A.B., Vogt, P.E., Kern, E.R., 1993. Evaluation of HPMPC therapy for primary and recurrent genital herpes in mice and guinea pigs. Antiviral Res. 21, 59–72.

Britt, W.J., 2006. Primate models: Pros and Cons. In: Reddehase, M.J. (Ed.), Cytomegalovirus, Molecular Biology and Immunology. Academic Press, Wymondham, UK, pp. 591–605.

Brown, J.M., Kaneshima, H., Mocarski, E.S., 1995. Dramatic interstrain differences in the replication of human cytomegalovirus in SCID-hu mice. J. Infect. Dis. 171, 1599–1603.

Bruggeman, C.A., Engels, W., Endert, J., 1987. Treatment of experimental cytomegalovirus infections with acyclovir. Arch. Virol. 97, 27–35.

Choi, Y.C., Hsiung, G.D., 1978. Cytomegalovirus infection in guinea pigs. II. Transplacental and horizontal transmission. J. Infect. Dis. 138, 197–202.

Chou, S., Lurain, N.S., Thompson, K.D., Miner, R.C., Drew, W.L., 2003. Viral DNA polymerase mutations associated with drug resistance in human cytomegalovirus. J. Infect. Dis. 188, 32–39.

Crippa, F., Corey, L., Chuang, E.L., Sale, G., Boeckh, M., 2001. Virological, clinical, and ophthalmologic features of cytomegalovirus retinitis after hematopoietic stem cell transplantation. Clin. Infect. Dis. 32, 214–219.

de Jong, M.D., Galasso, G.J., Gazzard, B., Griffiths, P.D., Jabs, D.A., Kern, E.R., Spector, S.A., 1998. Summary of the II International Symposium on Cytomegalovirus. Antiviral Res. 39, 141–162.

DiLoreto Jr., D., Epstein, L.G., Lazar, E.S., Britt, W.J., del Cerro, M., 1994. Cytomegalovirus infection of human retinal tissue: an in vivo model. Lab. Invest. 71, 141–148.

Duan, J., Paris, W., Kibler, P., Bousquet, C., Liuzzi, M., Cordingley, M.G., 1998. Dose and duration-dependence of ganciclovir treatment against murine cytomegalovirus infection in severe combined immunodeficient mice. Antiviral Res. 39, 189–197.

Enright, H., Haake, R., Weisdorf, D., Ramsay, N., McGlave, P., Kersey, J., Thomas, W., McKenzie, D., Miller, W., 1993. Cytomegalovirus pneumonia after bone marrow transplantation. Risk factors and response to therapy. Transplantation 55, 1339–1346.

Epstein, L.G., Cvetkovich, T.A., Lazar, E., Dehlinger, K., Dzenko, K., del Cerro, C., del Cerro, M., 1992. Successful xenografts of second trimester human fetal brain and retinal tissue in the anterior chamber of the eye of adult immunosuppressed rats. J. Neural Transplant Plast. 3, 151–158.

Erice, A., Borrell, N., Li, W., Miller, W.J., Balfour Jr., H.H., 1998. Ganciclovir susceptibilities and analysis of UL97 region in cytomegalovirus (CMV) isolates from bone marrow recipients with CMV disease after antiviral prophylaxis. J. Infect. Dis. 178, 531–534.

Fong, C.K., Cohen, S.D., McCormick, S., Hsiung, G.D., 1987. Antiviral effect of 9-(1,3-dihydroxy-2-propoxymethyl)guanine against cytomegalovirus infection in a guinea pig model. Antiviral Res. 7, 11–23.

Fowler, K.B., Boppana, S.B., 2006. Congenital cytomegalovirus (CMV) infection and hearing deficit. J. Clin. Virol. 35, 226–231.

Goodrich, J.M., Bowden, R.A., Fisher, L., Keller, C., Schoch, G., Meyers, J.D., 1993. Ganciclovir prophylaxis to prevent cytomegalovirus disease after allogeneic marrow transplant. Ann. Intern. Med. 118, 173–178.

Griffith, B.P., Chen, M., Isom, H.C., 1990. Role of primary and secondary maternal viremia in transplacental guinea pig cytomegalovirus transfer. J. Virol. 64, 1991–1997.

Griffith, B.P., Lucia, H.L., Bia, F.J., Hsiung, G.D., 1981. Cytomegalovirus-induced mononucleosis in guinea pigs. Infect. Immun. 32, 857–863.

Griffith, B.P., Lucia, H.L., Bia, F.J., Hsiung, G.D., 1982. Brain and visceral involvement during congenital cytomegalovirus infection of guinea pigs. Pediatr. Res. 16, 455–459.

Harrison, C.J., Myers, M.G., 1990. Relation of maternal CMV viremia and antibody response to the rate of congenital infection and intrauterine growth retardation. J. Med. Virol. 31, 222–228.

Jabs, D.A., Enger, C., Dunn, J.P., Forman, M., 1998. Cytomegalovirus retinitis and viral resistance: ganciclovir resistance. J. Infect. Dis. 177, 770–773.

Jabs, D.A., Martin, B.K., Forman, M.S., Ricks, M.O., 2005. Cytomegalovirus (CMV) blood DNA load, CMV retinitis progression and occurrence of resistant CMV in patients with CMV retinitis. J. Infect. Dis. 192, 640–649.

Kaptein, S.J.F., Vink, C., Bruggeman, C.A., Stassen, F.R.M., 2006. The rat model for CMV infection and vascular disease. In: Reddechase, M.J. (Ed.), Cytomegaloviruses: Pathogenesis, Molecular Biology, and Immunology. Horizon Scientific Press Ltd., Wymond, UK, pp. 501–523.

Kemble, G.W., Duke, G.M., Mocarski, E.S., 1999. Human cytomegalovirus infection of the SCID-hu (Thy/Liv) mouse. In: Zak, O., Sande, M.A. (Eds.), Handbook of Animal Models of Infection. Academic Press, London, United Kingdom, pp. 951–956.

Kern, E.R., 1991. Value of animal models to evaluate agents with potential activity against human cytomegalovirus. Transplant Proc. 23, 152–155.

Kern, E.R., 1997. Preclinical evaluation of antiviral agents. In: Galasso, G.J., Whitley, R.J., Merigan, T.C. (Eds.), Antiviral Agents and Human Viral Diseases, fourth ed. Raven Press, New York, NY, pp. 79–111.

Kern, E.R., 1999. Animal model for CMV infections: murine CMV. In: Zak, O., Sande, M.A. (Eds.), Handbook of Animal Models of Infection. Academic Press, London, United Kingdom, pp. 927–934.

Kern, E.R., Bidanset, D.J., Hartline, C.B., Yan, Z., Zemlicka, J., Quenelle, D.C., 2004a. Oral activity of a methylenecyclopropane analog, cyclopropavir, in animal models for cytomegalovirus infections. Antimicrob. Agents Chemother. 48, 4745–4753.

Kern, E.R., Collins, D.J., Wan, W.B., Beadle, J.R., Hostetler, K.Y., Quenelle, D.C., 2004b. Oral treatment of murine cytomegalovirus infections with ether lipid esters of cidofovir. Antimicrob. Agents Chemother. 48, 3516–3522.

Kern, E.R., Hartline, C.B., Rybak, R.J., Drach, J.C., Townsend, L.B., Biron, K.K., Bidanset, D.J., 2004c. Activities of benzimidazole D- and L-ribonucleosides in animal models of cytomegalovirus infections. Antimicrob. Agents Chemother. 48, 1749–1755.

Kern, E.R., Rybak, R.J., Hartline, C.B., Bidanset, D.J., 2001. Predictive efficacy of SCID-hu mouse models for treatment of human cytomegalovirus infections. Antiviral Chem. Chemother. 12 (Suppl. 1), 149–156.

Kimberlin, D.W., Lin, C.-Y., Sanchez, P.J., Demmler, G.J., Dankner, W., Shelton, M., Jacobs, R.F., Vaudry, W., Pass, R.F., Kiell, J.M., Soong, S.-J., Whitley, R.J., 2003. Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus desease involving the central nervous system: a randomized controlled trial. J. Pediatr. 143, 16–25.

Kushner, N.L., Williams, S.L., Hartline, C.B., Harden, E.H., Bidanset, D.J., Chen, X., Zemlicka, J., Kern, E.R., 2003. Efficacy of methylenecyclopropane analogs of nucleosides against herpesvirus replication in vitro. Nucleosides Nucleotides Nucleic Acids 22, 2105–2119.

Lalezari, J.P., Kuppermann, B.D., 1997. Clinical experience with cidofovir in the treatment of cytomegalovirus retinitis. J. Acquir. Immune Defic. Syndr. Hum. Retrovirol. 14 (Suppl. 1), S27–S31.

Laycock, K.A., Fenoglio, E.D., Hook, K.K., Pepose, J.S., 1997. An in vivo model of human cytomegalovirus retinal infection. Am. J. Ophthalmol. 124, 181–189.

Li, S.B., Yang, Z.H., Feng, J.S., Fong, C.K.Y., Lucia, H.L., Hsiung, G.D., 1990. Activity of (*S*)-1-(3-hydroxy-2-phosphonylmethoxypropyl) cytosine (HPMPC) against guinea pig cytomegalovirus infection in cultured cells and in guinea pigs. Antiviral Res. 13, 237–252.

Limaye, A.P., Corey, L., Koelle, D.M., Davis, C.L., Boeckh, M., 2000. Emergence of ganciclovir-resistant cytomegalovirus disease among recipients of solid-organ transplants. Lancet 356, 645–649.

Limaye, A.P., Raghu, G., Koelle, D.M., Ferrenberg, J., Huang, M.L., Boeckh, M., 2002. High incidence of ganciclovir-resistant cytomegalovirus infection among lung transplant recipients receiving preemptive therapy. J. Infect. Dis. 185, 20–27.

Ljungman, P., 2002. Beta-herpesvirus challenges in the transplant recipient. J. Infect. Dis. 186 (Suppl. 1), S99–S109.

Lowance, D., Neumayer, H.H., Legendre, C.M., Squifflet, J.P., Kovarik, J., Brennan, P.J., Norman, D., Mendez, R., Keating, M.R., Coggon, G.L., Crisp, A., Lee, I.C., 1999. Valacyclovir for the prevention of cytomegalovirus disease after renal transplantation. International Valacyclovir Cytomegalovirus Prophylaxis Transplantation Study Group. N. Engl. J. Med. 340, 1462–1470.

Lucia, H.L., Griffith, B.P., Hsiung, G.D., 1984. Effect of acyclovir and phosphonoformate on cytomegalovirus infection in guinea pigs. Intervirology 21, 141–149.

Meyers, J.D., Flournoy, N., Thomas, E.D., 1986. Risk factors for cytomegalovirus infection after human marrow transplantation. J. Infect. Dis. 153, 478–488.

Mocarski, E.S., Bonyhadi, M., Salimi, S., McCune, J.M., Kaneshima, H., 1993. Human cytomegalovirus in a SCID-hu mouse: thymic epithelial cells are prominent targets of viral replication. Proc. Natl. Acad. Sci. U. S. A. 90, 104–108.

Nelson, C.T., Demmler, G.J., 1997. Cytomegalovirus infection in the pregnant mother, fetus, and newborn infant. Clin. Perinatol. 24, 151–160.

Neyts, J., Balzarini, J., Naesens, L., De Clercq, E., 1992. Efficacy of (*S*)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine and 9-(1,3-dihydroxy-2-propoxymethyl)guanine for the treatment of murine cytomegalovirus infection in severe combined immunodeficiency mice. J. Med. Virol. 37, 67–71.

Nigro, G., Adler, S.P., La Toree, R., Best, A.M., Congenital Cytomegalovirus Collaborating Group, 2005. Passive immunization during pregnancy for congenital cytomegalovirus infection. N. Engl. J. Med. 353, 1350–1362.

O'Sullivan, C.E., Drew, W.L., McMullen, D.J., Miner, R., Lee, J.Y., Kaslow, R.A., Lazar, J.G., Saag, M.S., 1999. Decrease of cytomegalovirus replication in human immunodeficiency virus infected-patients after treatment with highly active antiretroviral therapy. J. Infect. Dis. 180, 847–849.

Palella Jr., F.J., Delaney, K.M., Moorman, A.C., Loveless, M.O., Fuhrer, J., Satten, G.A., Aschman, D.J., Holmberg, S.D., 1998. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. N. Engl. J. Med. 338, 853–860.

Pari, G.S., Netski, D., St Jeor, S., McCarthy, D., Smith, J., Georgio, D., von Hofe, E., 1998. Generation of a nude mouse tumor model for in vivo replication of human cytomegalovirus. J. Infect. Dis. 177, 523–528.

Paya, C.V., Wilson, J.A., Espy, M.J., Sia, I.G., DeBernardi, M.J., Smith, T.F., Patel, R., Jenkins, G., Harmsen, W.S., Vanness, D.J., Wiesner, R.H., 2002. Preemptive use of oral ganciclovir to prevent cytomegalovirus infection in liver transplant patients: a randomized, placebo-controlled trial. J. Infect. Dis. 185, 854–860.

Polis, M.A., Spooner, K.M., Baird, B.F., Manischewitz, J.F., Jaffe, H.S., Fisher, P.E., Falloon, J., Davey Jr., R.T., Kovacs, J.A., Walker, R.E., Whitcup, S.M., Nussenblatt, R.B., Lane, H.C., Masur, H., 1995. Anticytomegaloviral activity and safety of cidofovir in patients with human immunodeficiency virus infection and cytomegalovirus viruria. Antimicrob. Agents Chemother. 39, 882–886.

Razonable, R.R., Paya, C.V., 2003. Herpesvirus infections in transplant recipients: current challenges in the clinical management of cytomegalovirus and Epstein-Barr virus infection. Herpes 10, 60–65.

Reed, J.B., Schwab, I.R., Gordon, J., Morse, L.S., 1997. Regression of cytomegalovirus retinitis associated with protease-inhibitor treatment in patients with AIDS. Am. J. Ophthalmol. 124, 199–205.

Reynolds, D.W., Stagno, S., Stubbs, K.G., Dahle, A.J., Livingston, M.M., Saxon, S.S., Alford, C.A., 1974. Inapparent congenital cytomegalovirus infection with elevated cord IgM levels. Casual relation with auditory and mental deficiency. N. Engl. J. Med. 290, 291–296.

Ringden, O., Lonnqvist, B., Paulin, T., Ahlmen, J., Klintmalm, G., Wahren, B., Lernestedt, J.O., 1986. Pharmacokinetics, safety and preliminary clinical experiences using foscarnet in the treatment of cytomegalovirus infections in bone marrow and renal transplant recipients. J. Antimicrob. Chemother. 17, 373–387.

Rybak, R.J., Hartline, C.B., Qiu, Y.L., Zemlicka, J., Harden, E., Marshall, G., Sommadossi, J.P., Kern, E.R., 2000. In vitro activities of methylenecyclopropane analogues of nucleosides and their phosphoralaninate prodrugs against cytomegalovirus and other herpesvirus infections. Antimicrob. Agents Chemother. 44, 1506–1511.

Rybak, R.J., Zemlicka, J., Qiu, Y.L., Hartline, C.B., Kern, E.R., 1999. Effective treatment of murine cytomegalovirus infections with methylenecyclopropane analogues of nucleosides. Antiviral Res. 43, 175–188.

Safrin, S., Cherrington, J., Jaffe, H.S., 1997. Clinical uses of cidofovir. Rev. Med. Virol. 7, 145–156.

Schleiss, M.R., Bernstein, D.I., McVoy, M.A., Stroup, G., Bravo, F., Creasy, B., McGregor, A., Henninger, K., Hallenberger, S., 2005. The nonnucleoside antiviral, BAY 38-4766, protects against cytomegalovirus (CMV) disease and mortality in immunocompromised guinea pigs. Antiviral Res. 65, 35–43.

Schleiss, M.R., Anderson, J.L., McGregor, A., 2006. Cyclic cidofovir (HPMPC) prevents congenital cytomegalovirus infection in a guinea pig model. Virol. J. 3, 9.

Schleiss, M.R., Lacayo, J.C., 2006. The guinea pig model of congenital CMV infection. In: Reddehase, M.J. (Ed.), Cytomegaloviruses: Pathogenesis, Molecular Biology and Immunology. Horizon Scientific Press Ltd., Wymondham, Norfolk, UK, pp. 525–550.

Shanley, J.D., Pesanti, E.L., 1985. The relation of viral replication to interstitial pneumonitis in murine cytomegalovirus lung infection. J. Infect. Dis. 151, 454–458.

Smee, D.F., Morris, J.L., Leonhardt, J.A., Mead, J.R., Holy, A., Sidwell, R.W., 1992. Treatment of murine cytomegalovirus infections in severe combined immunodeficient mice with ganciclovir, (*S*)-1-[3-hydroxy-2-(phosphonylmethoxy)propyl]cytosine, interferon, and bropirimine. Antimicrob. Agents Chemother. 36, 1837–1842.

Smee, D.F., Sugiyama, S.T., Reist, E.J., 1994. Nucleotide analogs related to acyclovir and ganciclovir are effective against murine cytomegalovirus infections in BALB/c and severe combined immunodeficient mice. Antimicrob. Agents Chemother. 38, 2165–2168.

Stals, F.S., 1999. Animal models for cytomegalovirus infections: rat CMV. In: Zak, O., Sande, M.A. (Eds.), Handbook of Animal Models of Infection. Academic Press, San Diego, pp. 943–950.

Stals, F.S., Bosman, F., van Boven, C.P., Bruggeman, C.A., 1990. An animal model for therapeutic intervention studies of CMV infection in the immunocompromised host. Arch. Virol. 114, 91–107.

Stals, F.S., de Clercq, E., Bruggeman, C.A., 1991. Comparative activity of (*S*)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine and 9-(1,3-dihydroxy-2-propoxymethyl)guanine against rat cytomegalovirus infection in vitro and in vivo. Antimicrob. Agents Chemother. 35, 2262–2266.

Stals, F.S., Zeytinoglu, A., Havenith, M., De Clercq, E., Bruggeman, C.A., 1993. Rat cytomegalovirus-induced pneumonitis after allogeneic bone marrow transplantation: effective treatment with (*S*)-1-(3-hydroxy-2-phosphonyl-methoxypropyl)cytosine. Antimicrob. Agents Chemother. 37, 218–223.

Tural, C., Romeu, J., Sirera, G., Andreu, D., Conejero, M., Ruiz, S., Jou, A., Bonjoch, A., Ruiz, L., Arno, A., Clotet, B., 1998. Long-lasting remission of cytomegalovirus retinitis without maintenance therapy in human immunodeficiency virus-infected patients. J. Infect. Dis. 177, 1080–1083.

Wang, L.H., Peck, R.W., Yin, Y., Allanson, J., Wiggs, R., Wire, M.B., 2003. Phase I safety and pharmacokinetic trials of 1263W94, a novel oral anti-human cytomegalovirus agent, in healthy and human immunodeficiency virus-infected subjects. Antimicrob. Agents Chemother. 47, 1334–1342.

Weber, O., Reefschlager, J., Rubsamen-Waigmann, H., Raddatz, S., Hesseling, M., Habich, D., 2000. A novel peptide aldehyde with activity against human cytomegalovirus in two different in vivo models. Antiviral Chem. Chemother. 11, 51–59.

Williams, S.L., Hartline, C.B., Kushner, N.L., Harden, E.A., Bidanset, D.J., Drach, J.C., Townsend, L.B., Underwood, M.R., Biron, K.K., Kern, E.R., 2003. In vitro activities of benzimidazole D- and L-ribonucleosides against herpesviruses. Antimicrob. Agents Chemother. 47, 2186–2192.

Winston, D.J., Ho, W.G., Bartoni, K., Du Mond, C., Ebeling, D.F., Buhles, W.C., Champlin, R.E., 1993. Ganciclovir prophylaxis of cytomegalovirus infection and disease in allogeneic bone marrow transplant recipients. Results of a placebo-controlled, double-blind trial. Ann. Intern. Med. 118, 179–184.

Winston, D.J., Ho, W.G., Bartoni, K., Holland, G.N., Mitsuyasu, R.T., Gale, R.P., Busuttil, R.W., Champlin, R.E., 1988. Ganciclovir therapy for cytomegalovirus infections in recipients of bone marrow transplants and other immunosuppressed patients. Rev. Infect. Dis. 10 (Suppl. 3), S547–S553.

Winston, D.J., Yeager, A.M., Chandrasekar, P.H., Snydman, D.R., Petersen, F.B., Territo, M.C., 2003. Randomized controlled trial of oral ganciclovir and intravenous ganciclovir: prevention of cytomegalovirus disease after allogeneic bone marrow transplantation. Clin. Infect. Dis. 36, 749–758.

Woolf, N.K., Koehrn, F.J., Harris, J.P., Richman, D.D., 1989. Congenital cytomegalovirus labyrinthitis, and sensorineural hearing loss in guinea pigs. J. Infect. Dis. 160, 929–937.

Woolf, N.K., Ochi, J.W., Silva, E.J., Sharp, P.A., Harris, J.P., Richman, D.D., 1988. Ganciclovir prophylaxis for cochlear pathophysiology during experimental guinea pig cytomegalovirus labyrinthitis. Antimicrob. Agents Chemother. 32, 865–872.

Yang, Z.H., Lucia, H.L., Tolman, R.L., Colonno, R.J., Hsiung, G.D., 1989. Effect of 2′-nor-cyclic GMP against guinea pig cytomegalovirus infection. Antimicrob. Agents Chemother. 33, 1563–1568.