

Selecting neonates with congenital cytomegalovirus infection for ganciclovir therapy

Koenraad Smets · Kris De Coen · Ingeborg Dhooge · Lieve Standaert · Sabrina Laroche · Ludo Mahieu · Noël Logghe · Veerle Cossey · An Boudewyns

Received: 12 February 2006 / Accepted: 9 May 2006
© Springer-Verlag 2006

Abstract

Objective The objective of this study is to look for evidence based or scientific guidelines for selection of newborns with congenital cytomegalovirus (CMV) infection that might benefit from treatment with ganciclovir.

Materials and methods A literature search was conducted involving the MEDLINE database and the Cochrane Collaboration Library. Abstracts were reviewed to select pertinent articles dealing with ganciclovir therapy in neonates. References from selected articles as well as from reviews were screened for additional relevant articles. In total, 13 case reports (16 patients in all), three descriptive uncontrolled studies (20 patients in all), two randomized

dose-comparative studies (54 patients in all) and one randomized controlled study (42 patients) were identified.

Observations All reported patients presented with central nervous system manifestation of CMV infection. Only the randomized controlled study showed a reduction of hearing deterioration in the treated group. Published predictors of hearing loss in congenitally CMV infected children allow identification of candidates that might benefit from treatment. Studies so far are promising but of insufficient number to make evidence based recommendations about indications for treatment of congenital CMV. As such, studies are very difficult to conduct and treatment of infants at high risk of hearing loss may appear justified. There is

Prepared for the Flemish Society of Pediatrics' Neonatology and Perinatal Epidemiology Working Group: Aerssens Peter, MD, department of Pediatrics, Virga Jesse Hospital, Hasselt, Belgium; Casaer Alexandra, MD, Neonatal Intensive Care Unit, St Jan Hospital, Bruges, Belgium; Cools Filip, MD, Neonatal Intensive Care Unit, Free University of Brussels, Brussels Belgium; Deloof Els, MD, department of Pediatrics, Heilig-Hart Hospital, Leuven, Belgium; Jeannin Philippe, MD, department of Pediatrics, Jan Palfijn Hospital, Gent, Belgium; Naulaers Gunnar, MD, PhD, Neonatal Intensive Care Unit, University Hospital Leuven, Leuven, Belgium; Peirens Geertrui, MD, Child & Family, Hasselt, Belgium; Schatteman Isabelle, MD, department of Otorhinolaryngology, St Augustinus Hospital, Wilrijk, Belgium; Van Laer Paul, MD, Namen, Belgium; Van Mol Christine, MD, Neonatal Intensive Care Unit, St Augustinus Hospital, Wilrijk, Belgium

K. Smets (✉) · K. De Coen
Neonatal Intensive Care Unit,
Ghent University Hospital,
De Pintelaan 185,
9000 Ghent, Belgium
e-mail: koenraad.smets@UGent.be

I. Dhooge
Department of Otorhinolaryngology,
Ghent University Hospital,
Ghent, Belgium

L. Standaert
Medical Pedagogic Institute Spermalie,
Bruges, Belgium

S. Laroche · L. Mahieu
Neonatal Intensive Care Unit, University Hospital of Antwerp,
Edegem, Belgium

N. Logghe
Department of Pediatrics, City Hospital,
Roeselare, Belgium

V. Cossey
Neonatal Intensive Care Unit, University Hospital Leuven,
Leuven, Belgium

A. Boudewyns
Department of Otorhinolaryngology,
University Hospital of Antwerp,
Edegem, Belgium

scientific data to help clinicians in selecting a subgroup of infants that is at higher risk of hearing deterioration and therefore might benefit the most from ganciclovir therapy.

Keywords Ganciclovir · Congenital cytomegalovirus infection · Treatment · Sensorineural hearing loss

Abbreviations

BERA	Brainstem evoked response audiometry
CMV	Cytomegalovirus
CASG	Collaborative antiviral study group
CI	Confidence interval
CNS	Central nervous system
CT	Computerized tomography
OR	Odds ratio
SNHL	Sensorineural hearing loss

Introduction

Cytomegalovirus (CMV) infection is the most common congenital infection in the developed world, affecting 0.5 to 1.3% of live born infants [21]. Approximately 10% of those children will be symptomatic at birth. Outcome of these infants is poor: there is substantial mortality and most survivors suffer from severe neurologic sequelae [23]. Five to seventeen percent of clinically asymptomatic patients may develop late sequelae including sensorineural hearing loss (SNHL), making congenital CMV infection as the probable leading non-genetic cause of SNHL in childhood [12, 31, 38]. Over the past ten years, ganciclovir, a nucleoside analogue used in transplant recipients and patients infected with human immunodeficiency virus, has been evaluated in the treatment of infants with congenital CMV infection. In vivo, ganciclovir is converted to ganciclovir triphosphate, which inhibits CMV DNA polymerases by competitively inhibiting the incorporation of deoxyguanosine triphosphate into elongating viral DNA [8]. After the release of pyrophosphate, ganciclovir monophosphate is incorporated into the end of a growing chain of viral DNA, slowing replication. The drug can be monophosphorylated to a certain extent by normal, uninfected or non-transfected cells, possibly explaining its cytotoxic side effects (myelosuppression) in human patients [39].

The aim of this study is to review the evidence for the treatment of congenital CMV infection with ganciclovir and to present, on behalf of the Flemish Society of Pediatrics' Neonatology and Perinatal Epidemiology Working Group, a proposal of consensus regarding the antiviral management of congenital CMV infection in Flanders. The Working Group, basically consisting of neonatologists, general pediatricians and representatives of Child & Family, was for the purpose of the study expanded to include three

otorhinolaryngologists (BA, DI, SI) specialized in hearing disorders, two neonatologist-infectiologists (CV, ML) and one pediatrician (SL) specialized in follow-up care of children with hearing disabilities.

Methods

Literature search involved the MEDLINE database and the Cochrane Collaboration Library. We used the basic search terms "ganciclovir", "novel antivirals", "congenital cytomegalovirus", "hearing loss", "treatment", "antiviral therapy", "congenital infection", and "outcome". Abstracts were reviewed to select pertinent articles dealing with ganciclovir therapy in neonates. Reference lists from selected articles as well as from reviews were hand searched for additional relevant literature.

The selected articles were grouped according to their quality of evidence in case reports, descriptive uncontrolled studies, randomized dose-comparative studies and randomized controlled trials, and were summarized and discussed by the members of the Working Group. Review articles were not retained for further analysis.

Results

The National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group (CASG) conducted the first and, until now, only randomized, controlled trial of ganciclovir therapy in children with symptomatic congenital CMV disease [15]. All children had one or more of the following consequences of central nervous system (CNS) involvement: microcephaly, intracranial calcifications, cerebrospinal fluid abnormalities, chorioretinitis, impaired hearing. Ganciclovir was started within the first month of life at 12 mg/kg/day IV for 6 weeks. The primary endpoint was improved brainstem evoked response audiometry (BERA) between baseline and follow-up, or, for patients with normal baseline hearing, normal BERA at both time points. The results were subdivided in functional evaluation (results with the best ear) and biological evaluation (results with each individual ear), the latter representing the biological effects of ganciclovir therapy. Functional evaluation at six months and one year showed significantly less hearing deterioration in treated infants (0% and 21% respectively) than in non-treated infants (41% and 68% respectively) ($P < .01$ at both ages). Biological evaluation showed significantly more ears of infants in the treated group that maintained normal hearing or improved their hearing compared to ears of non-treated infants. There is no subgroup analysis within the treated group to identify those babies who would most likely benefit from ganciclovir

treatment. Among the ganciclovir recipients, a higher percentage of nonevaluable patients were born prematurely. This might have favoured a good outcome in the treatment group. Neutropenia occurred more frequently (63%) in the treated group than in control patients (21%). As the authors pointed out, the large proportion of unevaluable patients (58 of 100 subjects enrolled) raises concerns about follow-up bias and weakens the strength of their conclusions.

We further identified 13 case reports, comprising 16 children in all [1, 3, 11, 13, 14, 18, 26, 29, 30, 32, 34–36], three case series [19, 28, 33] together including 20 patients, and present data from two larger studies, comparing different treatment regimens.

Nigro et al. [22] compared two regimens of ganciclovir treatment started within the first 2 weeks of life in two small groups of neonates with congenital CMV infection. From the 12 children included in the study, seven had microcephaly (five of whom showed periventricular calcifications), five had chorioretinitis, five showed hypotonia, whereas four presented with hypertonia, and three babies suffered from convulsions. Group 1 (six children) was treated with ganciclovir 5 mg/kg twice daily for two weeks. Group 2 (six children) was treated with ganciclovir 7.5 mg/kg twice daily for 2 weeks, followed by 10 mg/kg three times a week for 3 months. In group 1 viral shedding disappeared in 3/6 infants, where in group 2 all six infants showed cessation of viraemia. In all babies viral shedding reappeared after treatment was discontinued. In group 1, two out of six babies showed a normal neurologic development at the age of 18 months; they both had become CMV-negative during treatment. In group 2, four out of six babies showed normal neurological outcome at age 18 months. In one of them microcephaly had disappeared; it is not mentioned if at birth that baby was a truly microcephalic appropriate for gestational age baby or a small for dates baby with symmetrically small head circumference. Two babies with initial chorioretinitis had normal eye examination at 18 months. Patients in the low-dose-short-duration regimen showed no side-effects. Side-effects in the higher-dose-longer-duration regimen were neutropenia (2/6 patients), elevated liver enzymes (2/6 patients) and difficulties for venous access (1/6 patients). Hematological side-effects were all transient. Long term complications related to the use of ganciclovir were not mentioned. Three patients (two in group 1 and one in group 2) had hearing loss on follow-up, but there were no data on hearing before treatment.

A larger phase II study compared two 6-weeks-regimens (8 mg/kg/day versus 12 mg/kg/day, in 14 and 28 babies, respectively) for toxicity, virologic response and clinical outcome [37]. Clinical evidence of CNS disease was one of the enrollment criteria. The 12 mg/kg/day group showed a more pronounced antiviral effect in urine. However, in all children viral shedding in urine reappeared following

discontinuation of antiviral therapy. The clearance of virus in urine correlated with normal neurologic examinations at 1 year ($r=.63$, $P=.036$). It is not mentioned if this correlation persisted at the age of 2 years and beyond. Audiologic data were available for 30 of 42 children and did not differ by treatment group. From 13 babies with normal baseline hearing, 11 became abnormal despite treatment. Details on the degree of deterioration are not mentioned. From 17 babies with abnormal baseline hearing, three had normal hearing on follow-up. It is not mentioned to which treatment group they belonged. Of 14 children with retinitis at baseline (two in the 8 mg/kg group, 12 in the 12 mg/kg group) eight had complete normalization at 6 months. Three babies developed retinal detachment; it was not specified whether retinopathy of prematurity was involved or not. Although this complication was not seen in the larger, randomized trial which was conducted later [15], it is still of concern in neonates with CMV retinitis. Of the children with normal ophthalmologic evaluation at baseline, three developed retinal scarring attributed to CMV. Eight (24%) of 33 children evaluated at ≥ 2 years met all developmental milestones and showed no neurologic impairment. Neurologic status did not differ by medication dose. The most significant aberrant laboratory parameters during therapy were abnormalities in neutrophil and platelet counts. Absolute neutropenia was more frequent with low dose (63%) than with high dose (19%). A moderate increase of creatinine (values > 2 mg/dl did not occur) was noted in 32%. Significant rise of liver enzymes (aspartate aminotransferase > 250 IU/dl; alanine aminotransferase > 150 IU/l) was noted in 36% in both groups.

Discussion

The problem when trying to interpret the results of the different reports published on the treatment of congenital CMV infection with ganciclovir is that they use different regimens of ganciclovir treatment (different dosages and different durations of therapy), different endpoints and different durations of follow-up. With these limitations in understanding the role of antiviral therapy one might want to restrict treatment to patients with severe or life- or sight-threatening end organ disease or with recurring or persisting disease [9].

All treated infants reported in literature presented with symptomatic congenital CMV infection, including in all cases at least one of the following consequences of CNS involvement: microcephaly, seizures, cerebrospinal fluid abnormalities, CNS imaging abnormalities (calcifications, periventricular echolucencies, cortical atrophy, dilated ventricles, echogenic enhancement in the caudothalamic grooves), SNHL, chorioretinitis. Other sonographic find-

ings in fetal cytomegalovirus infection of the brain include cystic leukomalacia, cerebellar vermis hypoplasia with large cisterna magna, intraventricular adhesions, and abnormal sulcation with or without hypoplastic corpus callosum [17]. There are no data on treatment of children without CNS manifestations, except for four patients who were treated for severe CMV pneumopathy [14, 34, 35]. However, 5% of asymptomatic congenitally infected children will present with SNHL, with a cumulative rate of 7.2% in the first 6 years of life [12]. Asymptomatic patients at increased risk for neurodevelopmental sequelae in general [16] and SNHL in particular [4] can be identified by measuring viral load in urine and/or blood. However, at this time antiviral treatment in this population cannot be recommended, but should be made part of a randomized clinical trial.

The one randomized controlled trial showed a clinically meaningful beneficial effect of ganciclovir treatment of symptomatic congenitally infected infants on hearing deterioration [15]. As no other studies have confirmed this finding, we feel the need for additional studies. However, conducting such studies is extremely difficult [24]. Eighteen centres took part in the enrollment in the trial of the National Institute of Allergy and Infectious Diseases CASG and it took them 8 years to complete the study [15].

For the individual patient, weighing of benefits and harms is necessary. Potential harms include hematological abnormalities, especially neutropenia, and catheter related problems, such as infection and catheter malfunction [15, 19, 22, 35, 37]. However, besides being a possible consequence of ganciclovir therapy, neutropenia and increased aminotransferase levels may be associated with active CMV infection, which causes neutrophil infection and liver involvement. Hematologic abnormalities are transient, but may necessitate dose adjustment or therapy interruption. Animal experiments with high doses of ganciclovir showed that short-term exposure induces testicular damage, affects sperm variables and may have carcinogenic effects [10, 39]. Thus, potential human toxicity is a real concern and plays a part in the consideration of whether or not to treat with ganciclovir. Kimberlin and colleagues are currently recruiting patients in a study to document pubertal development and cancer histories of study subjects enrolled in the CASG studies [2]. In the light of these potential complications, it would be of interest to identify a subgroup that is at high risk of hearing loss.

Several reports suggest a significant association between abnormalities detected on cerebral imaging and SNHL in symptomatic and asymptomatic children [5, 23, 27, 38]. In our personal experience some babies with congenital CMV infection show lenticulostriate vasculopathy or periventricular pseudocysts on cerebral ultrasound. Although these

findings can have other causes, in babies with proven congenital CMV infection we and others consider it as a manifestation of CNS involvement [17, 20, 40]. In the retained articles we found no babies with striatal vasculopathy who were treated with ganciclovir. Periventricular pseudocyst was reported in one article, but that baby also showed periventricular calcifications [13]. In the study of Williamson et al. [38], asymptomatic babies with periventricular radiolucencies on computerized tomography (CT) scan suffered significantly more from SNHL (4/13) than asymptomatic babies with normal CT scan (2/40). These data do not support the attitude to consider isolated striatal vasculopathy or an isolated single pseudocyst in a baby with congenital CMV infection as an indication to recommend ganciclovir therapy.

Logistic regression analysis of the data of 180 children with symptomatic congenital CMV infection showed that the presence of petechiae (OR: 2.8; 95% CI: 1.2–6.0) and intrauterine growth retardation (OR: 2.2; 95% CI: 1.4–6.2) were independently associated with the development of hearing loss [27]. Likewise, in a study of Bradford et al. [6], the presence of petechiae and viremia were independently associated with hearing loss. This suggests that children with disseminated disease regardless of whether they have CNS involvement could be candidates for antiviral therapy.

Microcephaly, after adjustment for weight deficit, has a 100% specificity (95% CI 84.5–100) for the prediction of mental retardation (intelligence quotient/developmental quotient <70) and/or major motor deficits (presence of motor abnormalities, such as hypertonia and spasticity, impairing the ability of the patient to perform tasks of daily living) [23]. On the other hand, it is not independently associated with an increased risk for SNHL [27]. There are no literature data suggesting that ganciclovir therapy would substantially improve prognosis in those patients. Even after cochlear implantation, children with motor and/or cognitive delay are significantly slower than other children in the development of speech perception skills [25]. Although we do not know this, perhaps treatment with ganciclovir might lead to better hearing in those severely neurologically impaired babies.

Until now, only two case reports provided pharmacokinetic data of oral treatment with valganciclovir, the valine ester of ganciclovir [18, 30]. The authors noted that continuous adaptation of dose was needed to achieve stable target plasma levels and to keep the viral load in urine at undetectable levels. Prospective studies to evaluate safety, efficacy and pharmacokinetics of valganciclovir in neonates are needed.

In conclusion, the Working Group proposes the following consensus: the major benefit from ganciclovir treatment in babies with congenital CMV might be a preservation of hearing, at least in the intermediate term. Evidence based

recommendations can not be extracted from literature. However, it seems possible to create a profile of the baby that might benefit the most from ganciclovir treatment. There is no literature data on treatment of asymptomatic children; this should only be done within the setting of a clinical trial. Such trial should preferably include asymptomatic babies with high viral load, as they are at higher risk of hearing loss. Babies with CNS manifestations of CMV infection (excluding isolated striatal vasculopathy and isolated single periventricular pseudocyst) and newborns with growth retardation and/or petechiae might be candidates for ganciclovir therapy. Those babies present with signs of disseminated disease, the latter two groups (growth retardation, petechiae) being clearly at higher risk of hearing loss. The Working Group members feel that newborns with severe hearing loss who repeatedly reach thresholds of ≥ 100 dB at BERA audiometry should not be treated with ganciclovir. Even with some improvement in hearing abilities, they are very likely to need cochlear implants anyway. We apply the treatment regimen as used by the CASG: ganciclovir 6 mg/kg/dose IV q 12 hours \times 6 weeks [15, 37]. Uncontrolled case series advocate a more prolonged course of therapy for optimal outcome, partially with oral valganciclovir and apparently without higher risk of side effects [7, 19, 22, 28]. At this time, however, by lack of controlled trials, there is no evidence for longer treatment. Oral treatment with valganciclovir should be limited to clinical trials, which should include pharmacokinetic data gathering and viral load determination in urine as a marker of drug efficacy.

We accept that there is no strong evidence base for our opinion, so ideally all babies should be included in prospective randomized trials. Given the progressive nature of sequelae associated with congenital CMV infection, long-term follow-up is mandatory. Such studies should be conducted preferably in a multicentre fashion in order to get results within an acceptable period of time. When patients are treated outside such trials, careful follow-up and communication of gathered data still may contribute to the evolving body of knowledge about ganciclovir therapy for congenital CMV infection.

References

- Attard-Montalto SP, English MC, Stimmler L, Snodgrass GJ (1993) Ganciclovir treatment of congenital cytomegalovirus infection: a report of two cases. *Scand J Infect Dis* 25:385–388
- NIAID (2005) Neonatal CMV-ganciclovir follow-up study. Available at: <http://www.clinicaltrials.gov/ct/show/NCT00031421>. Accessed 1 June 2006
- Barampouti F, Rajan M, Aclimandos W (2002) Should active CMV retinitis in non-immunocompromised newborn babies be treated? *Br J Ophthalmol* 86:248–249
- Boppana SB, Fowler KB, Pass RF, Rivera LB, Bradford RD, Lakeman FD, Britt WJ (2005) Congenital cytomegalovirus infection: association between virus burden in infancy and hearing loss. *J Pediatr* 146:817–823
- Boppana SB, Fowler KB, Vaid Y, Hedlund G, Stagno S, Britt WJ, Pass RF (1997) Neuroradiographic findings in the newborn period and long-term outcome in children with symptomatic congenital cytomegalovirus infection. *Pediatrics* 99:409–414
- Bradford RD, Cloud G, Lakeman AD, Boppana S, Kimberlin DW, Jacobs R, Demmler G, Sanchez P, Britt W, Soong S-j, Whitley RJ, National Institute of Allergy and Infectious Disease Collaborative Antiviral Study Group (2005) Detection of cytomegalovirus DNA by polymerase chain reaction is associated with hearing loss in newborns with symptomatic congenital CMV infection involving the central nervous system. *J Infect Dis* 191:227–233
- Burri M, Wiltshire H, Kahlert C, Wouters G, Rudin C (2004) Oral valganciclovir in children: single dose pharmacokinetics in a six-year-old girl. *Pediatr Infect Dis J* 23:263–266
- Crumpacker CS (1996) Ganciclovir. *N Engl J Med* 335:721–729
- Demmler GJ (2003) Congenital cytomegalovirus infection treatment. *Pediatr Infect Dis J* 23:1005–1006
- Faqi AS, Klug A, Merker HJ, Chahoud I (1997) Ganciclovir induces reproductive hazards in male rats after short-term exposure. *Hum Exp Toxicol* 16:505–511
- Fischler B, Casswall TH, Malmberg P, Nemeth A (2002) Ganciclovir treatment in infants with cytomegalovirus infection and cholestasis. *J Pediatr Gastroenterol Nutr* 34:154–157
- Fowler KB, McCollister FP, Dahle AJ, Boppana S, Britt WJ, Pass RF (1997) Progressive and fluctuating sensorineural hearing loss in children with asymptomatic congenital cytomegalovirus infection. *J Pediatr* 130:624–630
- Guimaraes H, Trindade E, Mateus M, d'Orey C, Almeida A, Martins A, Souto A, Teixeira Santos N (1996) Traitement par ganciclovir des infections congénitales à cytomégalo-virus. *Arch Pédiatr* 3:609–610
- Hocker JR, Cook LN, Adams G, Rabalais GP (1990) Ganciclovir therapy of congenital cytomegalovirus pneumonia. *Pediatr Infect Dis J* 9:743–745
- Kimberlin DW, Lin C, Sánchez PJ, Demmler GJ, Dankner W, Shelton M, Jacobs RF, Vaudry W, Pass RF, Kjell JM, Soong S-J, Whitley RJ, National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group (2003) Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: a randomized, controlled trial. *J Pediatr* 143:16–25
- Lanari M, Lazzorotto T, Venturi V, Papa I, Gabrielli L, Guerra B, Landini MP, Faldella G (2006) Neonatal cytomegalovirus blood load and risk of sequelae in symptomatic and asymptomatic congenitally infected newborns. *Pediatrics* 117:e76–e83
- Malinger G, Lev D, Zahalka N, Ben Aroia Z, Watemberg N, Kidron D, Ben Sira L, Lerman-Sagie T (2003) Fetal cytomegalovirus infection of the brain: the spectrum of sonographic findings. *Am J Neuroradiol* 24:28–32
- Meine Jansen CF, Toet MC, Rademaker CM, Ververs TF, Gerards LJ, van Loon AM (2005) Treatment of symptomatic congenital cytomegalovirus infection with valganciclovir. *J Perinat Med* 33:364–366
- Michaels MG, Greenberg DP, Sabo DL, Wald ER (2003) Treatment of children with congenital cytomegalovirus infection with ganciclovir. *Pediatr Infect Dis J* 22:504–508
- Mittendorf R, Kuban K, Pryde PG, Gianopoulos JG, Yousefzadeh D (2005) Antenatal risk factors associated with the development of lenticulostriate vasculopathy in neonates. *J Perinatol* 25:101–107
- Naessens A, Casteels A, Decatte L, Foulon W (2005) A serologic strategy for detecting neonates at risk for congenital cytomegalovirus infection. *J Pediatr* 146:194–197

22. Nigro G, Scholz H, Bartmann U (1994) Ganciclovir therapy for symptomatic congenital cytomegalovirus infection in infants: a two-regimen experience. *J Pediatr* 124:318–322
23. Noyola DE, Demmler GJ, Nelson CT, Griesser C, Williamson WD, Atkins JT, Rozelle J, Tutcich M, Llorente AM, Sellers-Vinson S, Reynolds A, Bale JF, Gerson P, Yow MD, Houston Congenital CMV Longitudinal Study Group (2001) Early predictors of neurodevelopmental outcome in symptomatic congenital cytomegalovirus infection. *J Pediatr* 138:325–331
24. Prober CG, Enright AM (2003) Congenital cytomegalovirus infections: hats off to Alabama. *J Pediatr* 143:4–6
25. Pyman B, Blamey P, Lacy P, Clark G, Dowell R (2000) The development of speech perception in children using cochlear implants: effects of etiologic factors and delayed milestones. *Am J Otol* 21:57–61
26. Reigstad H, Bjerknes R, Markestad T, Myrmed H (1992) Ganciclovir therapy of congenital cytomegalovirus disease. *Acta Paediatr* 81:707–708
27. Rivera LB, Boppana SB, Fowler KB, Britt WJ, Stagno S, Pass RF (2002) Predictors of hearing loss in children with symptomatic congenital cytomegalovirus infection. *Pediatrics* 110:762–767
28. Rojo P, Ramos JT (2004) Ganciclovir treatment of children with congenital cytomegalovirus infection. *Pediatr Infect Dis J* 23:88–89
29. Sampath V, Narendran V, Donovan EF, Stanek J, Schleiss MR (2005) Nonimmune hydrops fetalis and fulminant fatal disease due to congenital cytomegalovirus infection in a premature infant. *J Perinatol* 25:608–611
30. Schulzke S, Bühner C (2006) Valganciclovir for treatment of congenital cytomegalovirus infection. *Eur J Pediatr* (epub ahead of print) DOI 10.1007/s00431-006-0109-0
31. Smith RJH, Bale JF Jr, White KR (2005) Sensorineural hearing loss in children. *Lancet* 365:879–890
32. Stronati M, Revello MG, Cerbo RM, Furione M, Rondini G, Gerna G (1995) Ganciclovir therapy of congenital human cytomegalovirus hepatitis. *Acta Paediatr* 84:340–341
33. Tanaka-Kitajima N, Sugaya N, Futatani T, Kanegane H, Suzuki C, Oshiro M, Hayakawa M, Futamura M, Morishima T, Kimura H (2005) Ganciclovir therapy for congenital cytomegalovirus infection in six infants. *Pediatr Infect Dis J* 24:782–785
34. Tricoire J, Rolland M, Regnier C (1993) Traitement par ganciclovir des infections congénitales à cytomégalo-virus. *Arch Fr Pediatr* 50:173
35. Vallejo JG, Englund JA, Garcia-Prats JA, Demmler GJ (1994) Ganciclovir treatment of steroid-associated cytomegalovirus disease in a congenitally infected neonate. *Pediatr Infect Dis J* 13:239–241
36. Weng YH, Chu SM, Lien RI, Chou YH, Lin TY (2003) Clinical experience with ganciclovir and anti-cytomegalovirus immunoglobulin treatment for a severe case of congenital cytomegalovirus infection. *Chang Gung Med J* 26:128–132
37. Whitley RJ, Cloud G, Gruber W, Storch GA, Demmler GJ, Jacobs RF, Dankner W, Spector SA, Starr S, Pass RF, Stagno S, Britt WJ, Alford C Jr, Soong S-J, Zhou X-J, Sherrill L, FitzGerald JM, Sommadossi J-P, and the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group (1997) Ganciclovir treatment of symptomatic congenital cytomegalovirus infection: results of a phase II study. *J Infect Dis* 75:1080–1086
38. Williamson WD, Demmler GJ, Percy AK, Catlin FI (1992) Progressive hearing loss in infants with asymptomatic congenital cytomegalovirus infection. *Pediatrics* 90:862–866
39. Wutzler P, Thust R (2001) Genetic risks of antiviral nucleoside analogues—a survey. *Antiviral Res* 49:55–74
40. Yamashita Y, Outani Y, Kawano Y, Horikawa M, Matsuishi T, Hashimoto T (1990) Clinical analyses and short-term prognoses of neonates with subependymal cysts. *Pediatr Neurol* 6: 375–378