

ORIGINAL RESEARCH

Efficacy of Valganciclovir versus Ganciclovir in treatment of symptomatic cytomegalovirus infection in infants: An open-label randomized controlled trial

Kanij Fatema¹, Md Mizanur Rahman¹, Shaheen Akhtar¹, Jannatara Shefa²

¹Department of Paediatric Neurology, Institute of Pediatric Neurodisorder and Autism (IPNA), Bangabandhu Sheikh Mujib Medical University, ² Institute of Paediatric Neurodisorder and Autism (IPNA), Bangabandhu Sheikh Mujib Medical University

Corresponding author: Jannatara Shefa; Email: shefaafnan@yahoo.com; Tel: +88-0171-5254283.

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Abstract

Introduction: Congenital cytomegalovirus (CMV) infection is the most common viral infection transmitted via the placenta, causing significant neurodevelopmental impairment in infants and children. Ganciclovir and Valganciclovir are two drugs used in the treatment of symptomatic CMV infected case which have limited comparative study. This study compared the efficacy and tolerability of these two drugs on symptomatic CMV infected infants. **Methodology:** This was an open-label randomized controlled trial done to compare oral valganciclovir (VGCV) with injectable ganciclovir (GCV) in the treatment of symptomatic congenital CMV infected infants. A total of 72 patients were included; 12 patients discontinued the treatment due to noncompliance or side effects. Pre and post-treatment CMV virus levels and adverse effects were monitored. Psychological, visual, and hearing assessments were performed at baseline and six months post-treatment. **Results:** The mean age of the infants in VGCV and GCV group was 7.10 ± 3.58 and 7.50 ± 3.99 months, respectively. Nineteen infants presented with developmental delay, 13 with seizure, 4 with a movement disorder. Twenty-one percent of the infants were preterm, and 38% were low birth weight. Eighteen infants had a neonatal seizure. Twenty-eight infants of VGCV and 24 infants of the GCV group showed clearance of the virus after six weeks of treatment. No statistical difference was found in virus clearance. Regarding ophthalmological assessment, infants had chorioretinitis, optic atrophy, squint, and cortical blindness. On hearing assessment, none of the infants deteriorated after drug administration, while some showed improved hearing. None of the infants showed deterioration of cognition, while some of the infants showed improvement in cognitive assessment, but there was no significant difference in two groups. The side effects of GCV were significantly greater than VGCV (P value < 0.05). **Conclusion:** In symptomatic congenital CMV infection in infants, VGCV is as efficient as GCV, and the former has fewer side effects.

Keywords: Congenital cytomegalovirus infection; Valganciclovir; Ganciclovir; Randomized controlled trial

Introduction

Cytomegalovirus (CMV) is the most common cause of congenital infections in humans. The prevalence of CMV is 0.2–2% (average of 0.64%) of pregnancies in the US, Canada, Australia, and Western Europe. Limited studies from developing countries have shown a prevalence ranging from 0.6 to 6.1% of pregnancies [1].

Primary maternal CMV infection carries a 30-40% risk of vertical transmission, with 0.2-2% of secondary infections

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leading to fetal infection [2]. Infection at an earlier gestational age often correlates with a less favorable outcome [3][4]. Only about 7 to 10% have a clinically evident disease at birth [5][6]. Jaundice (62%), petechiae (58%), and hepatosplenomegaly (50%) are the most frequently noted symptoms and constitute the classical triad of congenital CMV infection (cCMV) infection [7]. Central nervous system (CNS) involvement is present in approximately two-thirds of infants with symptomatic cCMV infection [8][9]. It is the leading nongenetic cause of sensorineural hearing

loss (SNHL) estimated to be responsible for one-third of all cases in children [10]. The other neurological consequences are mental retardation, seizures, psychomotor and speech delays, learning disabilities, chorioretinitis and optic nerve atrophy [11][12][13][14].

cCMV infection is defined as active CMV infection detectable within the first three weeks of life. Given the devastating sequelae of cCMV, it is recommended that treatment should be instituted in infants with cCMV with the following criteria: positive CMV DNA PCR plus evidence of central nervous system involvement, including SNHL and developmental delay, stigmata of CMV disease even after neonatal period in infancy, chorioretinitis and critically ill preterm infants with life-threatening CMV infection manifested by pneumonitis, hepatitis or encephalitis [10][15]. Ganciclovir (GCV) and Valganciclovir (VGCV) are the drugs used to treat cCMV. GCV is a synthetic acyclic nucleoside analogue, structurally similar to guanine [15]. GCV penetrates well into the CNS, a characteristic that makes it an important treatment agent in the setting of CMV-induced neurodevelopmental injury [16].

Although GCV appeared to be of value in the short-term management of CMV infection in infants in some settings, it is less clear whether the use of GCV provided any long-term benefit for congenitally or perinatally acquired CMV infection. Multicenter studies conducted by the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group (CASG) have shed light on the potential long-term benefits of antiviral therapy. These trials have focused on the impact of antiviral therapy on symptomatic cCMV infection with CNS involvement [17][18]. A subsequent phase II CASG study of GCV for symptomatic cCMV showed improvement or stabilization of hearing impairment in 5(16%) of 30 babies at six months or later, indicating efficacy [19]. On the other hand, studies on Valganciclovir (VGCV), a monoethyl ester prodrug that is rapidly hydrolyzed to GCV when taken orally, showed that VGCV has ten times greater oral bioavailability than oral GCV (53.6% vs. 4.8%) [20][?]. Kimberlin *et al.* showed in a study that 16 mg/kg dose of oral VGCV solution administered twice daily provided GCV concentration compared with that of 6 mg/kg/dose of IV GCV [21].

Intravenous administration of GCV necessitates prolonged hospital stay. The major side effect of GCV is hematologic, including leucopenia, neutropenia, and thrombocytopenia. Other rare side effects are bone marrow suppression, raised liver enzymes, hypokalemia, and renal impairment [22]. There are no definite guidelines on whether IV GCV or oral VGCV should be used for symptomatic cCMV infected infants. There are minimal studies regarding this, particularly in resource-limited settings where the problem is more prevalent. Whether the orally bioavailable VGCV is as effective as GCV in improving sensory hearing loss in symptomatic newborns still needs to be ascertained.

Methods

This study aimed to find out the efficacy and tolerability of VGCV and GCV in symptomatic CMV infected infants. This was an open-label randomized controlled trial conducted at a tertiary care paediatric neurology centre. Relevant permissions were obtained from the institutional Ethics Committee. The following formula was used to determine the sample size. All infants (0-1 year) who had a neurodevelop-

$$N = \frac{P1(1 - P1) + P2(1 - P2)}{(P1 - P2)^2} \times (Z\alpha - Z\beta)^2$$

mental deficit with evidence of CMV infection, as indicated by a urinary CMV DNA qPCR positivity within one month of attending the center during the study period, were included. More than 500 copies of the virus on real-time qPCR in urine samples was considered a positive result. The study period was from August 2015 to September 2016. Seventy-two patients were included, by randomization, with 39 patients in the GCV and 33 in the VGCV group. The primary study outcome was clearance of the virus from the body, and the secondary outcome was an improvement of hearing, vision, and psychological function.

A detailed medical history, including presenting complaints, birth history, antenatal history, and past history, was taken, followed by a general and systemic examination. Informed written consent was taken from the guardian or caregiver. Randomization was done by lottery method. GCV group was entitled as control and VGCV group was entitled as case. The terms GCV and VGCV were written on paper strips of the same size, shape, and color. They were folded and mixed up in a container. A blindfold selection was made with the required numbers of slips selected for the desired sample size. All enrolled infants underwent a baseline visual, hearing, and psychological assessment. Following drug treatment, visual, hearing, and psychological assessment was performed again at six months and compared to the initial assessment. Assessment of hearing included Brainstem Auditory-Evoked Responses (BAER)/Auditory Brainstem Responses (ABR) or Otoacoustic Emissions (OAEs). The hearing was ascertained as normal, mild, moderate, or severe impairment. An infant was tagged as improved or deteriorated based on improvement in hearing status and the psychological assessment using the mental scale of BSID-II (Baily Scale of Infant Development II) at baseline and six months following first administration of the drug [23].

VGCV was administered orally at 16 mg/kg/dose 12 hourly for 42 days and GCV, intravenously 6 mg/kg/dose 12 hourly for 42 days. 24 Infants who had chorioretinitis were treated for six months, but they were not included in the study protocol and are not discussed in this paper. In all the infants, urinary CMV qPCR was done at 6 weeks of drug treatment. Baseline and weekly complete blood count (CBC), Serum glutamic pyruvic transaminase (SGPT) and serum creatinine levels were done to determine any side effects. Other investigations were also performed based on

the clinical indication. Computed tomography (CT) or magnetic resonance imaging (MRI) was done to determine the extent of disease and exclude any other comorbid condition. In suspected cases, a metabolic panel was done to exclude a metabolic disorder.

Nine patients from the GCV group and three patients from the VGCV group discontinued treatment owing to noncompliance or adverse effects and dropped out of the study. Seven patients from GCV group dropped out due to adverse effects, including phlebitis (2) neutropenia (3) and hypersensitivity (2) reaction. In the VGCV group, one patient discontinued due to pancytopenia. Also, one patient from the GCV group and two patients from the VGCV arm discontinued due to personal issues. Infants with concomitant suspected neurometabolic or neurodegenerative disorder and preexisting renal disease or pancytopenia were excluded from the study.

Data were entered using SPSS (version 16.0) [24] and double-checked before analysis. Descriptive statistics such as frequency tabulation, mean, median, standard deviation, Chi-square test, and t-tests were performed to find out the test of significance. Statistical significance was fixed at a *P* value of <0.05.

Results

Study population: Overall seventy-two patients under one year of age were included in this study. Sixty of them completed six months of follow up and thus underwent outcome evaluation. Infants in the VGCV arm had significantly increased delay in motor development compared to the GCV group (*P*= 0.037). Demographic characteristics are shown in Table 1.

Clinical parameter: Infants presented with developmental delay, seizures, abnormal involuntary movements, visual and hearing impairment (see Table 2).

Perinatal status: The two study groups were not statistically different in terms of gestational age, birth weight, perinatal asphyxia, and neonatal presentation. However, the incidence of neonatal seizures was the same in both groups (30%) (see Table 3). **Clinical outcome:** After six months of treatment, no significant improvement was noted in visual status, although the number of infants with normal eye finding increased after treatment. Chorioretinitis resolved in five infants from the GVC group and in one infant from the VGCV group. Most infants in both groups had a mild form of hearing impairment. However, the number of infants returning to normal hearing was equal in both groups. No statistical difference was found in the cognitive status of the GCV recipients at six months follow up while the VGCV group showed a statistically significant improvement psychological status (*p* = 0.016) (Table 4) on the mental scale of BSID-II.

Clearance of virus: At six weeks of therapy, urinary CMV qPCR did not show any statistically different viral clearance between the two groups, although the clearance was higher

Table 1 Baseline characteristics of studied infants (N=60)

Baseline characteristics	Control (GCV) n=30 n(%)	Case (VGCV) n=30 n (%)	<i>P</i> value
Age (months)			
< 5	11(36.7%)	10(33.3%)	0.684 [†]
5-10	12(40.0%)	14(46.7%)	
> 10	7(23.3%)	6(20.0%)	
Mean±SD	7.50±3.99	7.10±3.58	
Sex			
Male	12(40.0%)	13(43.3%)	0.793 [†]
Female	18(60.0%)	17(56.7%)	
Gestational age			
Term	23(76.7%)	24(80.0%)	0.754 [†]
Preterm	7(23.3%)	6(20.0%)	
Birth weight			
Normal	17(56.7%)	16(53.3%)	0.491 [†]
LBW	10(33.3%)	13(43.3%)	
IUGR	3(10.0%)	1(3.3%)	
Milestones of development			
Age appropriate	3(10.0%)	8(26.7%)	0.037*
Motor delay	22(73.3%)	11(36.7%)	
Speech delay	1(3.3%)	1(3.3%)	
GDD	4(13.3%)	10(33.3%)	
Presenting complaints			
Developmental delay	7(23.3%)	12(40.0%)	0.168 [†]
Seizure	6(20.0%)	7(23.3%)	
Abnormal movement	1(3.3%)	3(10.0%)	
Multiple clinical features	16(53.3%)	8(26.7%)	
Total	30(100.0%)	30(100.0%)	
Perinatal asphyxia			
Yes	11(36.7%)	15(50.0%)	0.297 [†]
No	19(63.3%)	15(50.0%)	
Postnatal problems			
No	18(60.0%)	12(40.0%)	0.360 [†]
Neonatal seizure	9(30.0%)	9(30.0%)	
Infection	2(6.7%)	5(16.7%)	
Cardiac problem	3(10.0%)	2(6.7%)	
Neonatal jaundice	0(0.0%)	2(6.7%)	
Others	0(0.0%)	1(3.3%)	

[†]not significant; *significant; LBW Low Birth Weight; IUGR Intrauterine Growth Retardation

in the VGCV compared to the GCV group.

Adverse effect of drugs: GCV treated infants had phlebitis (16.7%), which was absent in the VGCV group as they had oral administration of the drug. In the GCV group, the most common side effect was infection (23.3%). However, there was a significant difference in the number of infants without any adverse effects between the two groups (VGCV 60% vs. GCV 23.3%) (*p* <0.5). Thus VGCV had more tolerability than GCV (Table 6). Overall, no significant difference was found in the control and case groups regarding virus clearance from urine, improvement of hearing, visual, and psychological status.

Discussion

CMV is the most common cause of congenital infections in humans and has a profound impact on infants' health. In-

Table 2 Distribution of studied infants by visual, auditory and psychological status before and after 6 month of intervention (N=60)

Parameters	Control (GCV) (n=30) N(%)		Case(VGCV) (n=30) N(%)	
	Before	After	Before	After
Visual status				
Normal	16(53.3%)	17(56.7%)	15(50.0%)	19(63.3%)
Chorioretinitis	5(16.7%)	4(13.3%)	7(23.3%)	2(6.7%)
Optic atrophy	5(16.7%)	5(16.7%)	6(20.0%)	6(20.0%)
Squint	1(3.3%)	1(3.3%)	0(0.0%)	0(0.0%)
Cataract	0(0.0)	0(0.0%)	0(0.0%)	1(3.3%)
Cortical blindness	1(3.3%)	1(3.3%)	2(6.7%)	2(6.7%)
Others	2(6.6%)	2(6.4%)	0(0.0%)	0(0.0%)
P value	0.999 [†]		0.373 [†]	
Auditory status				
Normal	12(40.0%)	18(60.0%)	17(56.7%)	21(70.0%)
Mild HI	7(23.3%)	5(16.7%)	11(36.7%)	6(20.0%)
Moderate HI	7(23.3%)	6(20.0%)	2(6.7%)	3(10.0%)
Severe HI	4(13.3%)	1(3.3%)	0(0.0%)	0(0.0%)
P value	0.884 [†]		0.351 [†]	
Psychological status				
Normal	4(13.3%)	7(23.3%)	1(3.3%)	8(26.7%)
Mild Impairment	15(50.0%)	17(56.7%)	17(56.7%)	17(56.7%)
Severe impairment	11(36.7%)	6(20.0%)	12(40.0%)	5(16.7%)
P value	0.229 [†]		0.016 [*]	

[†]not significant; ^{*}significant; HI Hearing impairment

Table 3 Adverse effects following drug treatment (tolerability) (N=60)

Adverse effects	Control (n=30)	Case (n=30)
No side effects*	7(23.3%)	18(60.0%)
Pancytopenia	0(0.0%)	1(3.3%)
Neutropenia	3(10.0%)	3(10.0%)
Anemia	4(13.3%)	3(10.0%)
Infection	7(23.3%)	3(10.0%)
Phlebitis	5(16.7%)	0(0.0%)
Hypersensitivity reaction	4(13.3%)	2(6.7%)
Total	30(100.0%)	30(100.0%)

*P=0.039

infants with CMV infection at birth have higher rates of hearing impairment and neurodevelopmental sequelae [25]. Even though there is a growing number of studies on CMV infection, there is no highly effective and safe antiviral therapy currently available for the treatment of cCMV infection. Clinical trials are in progress [26][27].

This study aimed to further contribute to studies undertaken in resource-limited settings. This open-label, randomized controlled study compared the efficacy and tolerability of VGCV and GCV in cCMV infected infants. Infants in both groups were comparable based on their baseline characteristics except for motor developmental delay, which was significantly higher in the VGCV treated infants (P=0.037).

Antenatal history is an important clue to diagnose cCMV infection. In this study, a very small number of infants had antenatal history findings of maternal fever, rash, or history of previous miscarriages. This is in keeping with a similar study done by Ehab Abd, where only 6% had similar

Table 4 Distribution of infants by effect of intervention (N=60)

Parameters	Control (n=30) n(%)	Case (n=30) n(%)	P value
Clearance of virus	24(80.0%)	28(93.3%)	0.128
Auditory status normalization	6(20.0%)	4(13.3%)	0.488
Visual status normalization	1(3.3%)	4(13.3%)	0.161
Chorioretinitis resolved	1(3.3%)	5(16.7%)	0.085
Cognitive status improved	5(16.7%)	7(23.3%)	0.518
Free from side effects	7(23.3%)	18(60.0%)	0.003*

*significant

clues in the antenatal history to suspect cCMV [28]. Post-natally, infants in this study had neonatal seizures (30%), infection (11.6%), cardiac problem (8.33%), neonatal jaundice (3.3%), developmental delay (31.6%), visual (45%) and hearing (51%) impairment. The results were in keeping with similar studies done by Suresh B. Boppana, Ornoy and Diav-Citrin [29][30].

CMV infection may cause impaired fetal growth. The risk of intrauterine transmission after primary CMV infection during pregnancy approaches 40%, with an increased risk of adverse fetal effects if infection occurs during the first half of pregnancy [31]. This has also been evidenced in this study. In the current study, the incidence of low birth weight (LBW) and intrauterine growth retardation (IUGR) were 38.3% and 6.6%, respectively, although it was not statistically significant. The results were in keeping with a similar study done by Yoshinaga-Itano et al. [32].

The clearance of virus from urine at six weeks of treatment was an important outcome parameter for this study. In the current study, 93.4% of VGCV treated infants showed clearance of virus from urine at six weeks, while only two infants (6.6%) showed nonclearance of the virus. On the contrary, in GCV treated infants, six infants (20%) showed nonclearance of the virus. However, there was no statistical difference between these two groups. Only limited clinical trials so far have compared the two drugs studied. In a related study done by Lombardi et al., 8 out of 12 newborns suffering from symptomatic cCMV who were treated with oral VGCV, 15 mg/kg every 12 hours for six weeks showed virus clearance while nonclearance of the virus was seen in 33.3% [33]. In another study where CMV infected infants were treated with the two regimens viral shedding disappeared in 3/6 infants treated with GCV 5 mg/kg twice daily for two weeks, While in the GCV group who received 7.5 mg/kg twice daily for two weeks, followed by 10 mg/kg three times a week for three months, all six infants showed cessation of viruria[34]. Thus the duration of the drug seemed to be a significant factor for clearance of the virus.

The majority of infants in both groups had mild cognitive impairment in this study (53.33%). It is known that infants with CMV infection are at risk of developmental delay, particularly in cognitive functioning [32][35]. The current study suggests that both GCV and VGCV treatment of cCMV infected infants resulted in the improvement of cognitive status. VGCV treated infants showed significantly im-

proved cognitive status at six months follow up ($P < 0.5$) as assessed by the BSID-II mental scale, while GCV treated infants showed no significant improvement in cognitive status. This observation was in keeping with other related studies. However, a study by Amir et al. who treated 23 infants with symptomatic cCMV infection with IV GCV followed by oral VGCV until the age of 12 months showed psychomotor retardation at age one year in 18% which was considerably lower than the 55% reported in the past [36]. In another study conducted in 100 neonates who were enrolled in a controlled trial, six weeks of intravenous GCV at 12 mg/kg/day was given compared to no antiviral treatment. The results showed that fewer treated subjects had neurodevelopmental delays compared to those who did not receive antiviral therapy [37]. However, no comparative randomized trial has been published comparing the efficacy of VGCV and GCV on the improvement of cognitive status. These studies however support the importance of treating CMV infected infants with antiviral drugs, which may result in improvement of cognitive status.

CMV infection can cause a spectrum of ocular manifestations. A substantial portion of infants in this study had abnormal eye findings, including chorioretinitis (20%), optic atrophy (18.33%), cortical blindness, and squint. These findings are in keeping with a related study where chorioretinitis, squint, and optic atrophy were the most common abnormalities [28][38]. Like most other studies, chorioretinitis was the commonest eye finding in CMV infected children. Treatment resulted in the improvement of visual function, although not statistically significant. Following VGCV treatment, five infants had resolution of chorioretinitis while in the GCV group, only one infant had a resolution of chorioretinitis. In another study from Bangladesh, Mahbub et al. also observed that while the visual function improved in a larger proportion of infants treated with ganciclovir, the results were not statistically significant [39]. In contrast to these observations, Shoji et al. showed statistically significant improvement or resolution of chorioretinitis in 50% of infants who were treated with IV GCV [40].

The prevalence of sensorineural hearing loss caused by cCMV infection (symptomatic and asymptomatic) at birth is 5.2%, and late-onset hearing loss at six years is 15.4% [12]. Previously several studies have shown that drug treatment either prevents deterioration of hearing status or improves it [39][41][42]. In the current study, no statistically significant difference was found at six months follow up in audiology assessments. Most infants in both groups had only mild hearing impairment. However, following treatment with VGCV at six months, the number of infants with normal hearing increased to 21(70.0%) from 17(56.7%). In one infant, the hearing loss deteriorated from mild to moderate. On the other hand, in the GCV group, only six infants had normal hearing following intervention.

No similar comparative study has been done with GCV and VGCV with regard to hearing status. A related study done by Lauren Nassetta et al. who treated infants with IV GCV found that there was either improvement or no dete-

rioration in hearing at six months follow up compared with no treatment group ($P = 0.06$) [43]. Lombardi et al., who treated symptomatic cCMV infants with oral VGCV, found that while there was no deterioration in hearing in any of the subjects, two infants demonstrated improved hearing status at 6 to 8 months follow-up [33]. In another randomized controlled trial, where GCV was given within the first month at 12 mg/kg/d intravenously for six weeks, twenty-one (84%) of 25 ganciclovir recipients demonstrated improved or maintained normal hearing at months compared to controls ($p = 0.06$). On follow up at 1 year or beyond only five (21%) of 24 subjects treated with ganciclovir had worsening of hearing compared to 13(68%) of 19 control patients ($P < 0.01$) [44]. The same researchers in a more recent study reported that infants receiving six months of VGCV therapy, compared with those receiving six weeks of VGCV treatment, have improved hearing outcomes [45].

The major toxicity in patients receiving GCV and VGCV is hematologic abnormalities, particularly neutropenia [22]. In the current study, adverse effects observed were neutropenia, anemia, infection, pancytopenia, hypersensitivity reaction, and phlebitis. In terms of adverse effects there was a significant difference between the two groups with 60% of VGCV recipients free from any adverse effects compared to 23.3% of the GCV recipients ($P < 0.05$). Also, infants who were treated with GCV had phlebitis (16.7%) as they had IV medication. No statistically significant difference was found in neutropenia (10.0%) in both groups. This is similar to findings from a related study where neutropenia was seen in 63% of infants with GCV therapy and 38% in VGCV treated infants. ($P > 0.5$).

Neutropenia related sepsis, however, was rarely a problem and dangerous neutropenia has rarely been described, and is easily resolved by diminishing drug doses or interrupting therapy for 3 -7 days [46]. Other rare side effects are bone marrow suppression, elevated liver enzymes, hypokalemia, and renal impairment which were not observed in the current study [19]. Seven infants in the GCV group and one infant in the VGCV group discontinued treatment owing to adverse effects, particularly fever due to neutropenia, phlebitis, and hypersensitivity. These infants were not included in the statistical analysis. Thus comparing the effect of intervention between the two drugs, VGCV recipients showed significantly improved psychological status, and a high proportion of patients did not show any adverse effects. The current study suggests that all infants with neurodevelopment deficits should be screened for CMV infection. CMV PCR positive infants should be treated with either GCV or VGCV, preferably VGCV, as the latter showed improved cognitive outcome and lesser side effects.

Conclusion

From the present study, it can be concluded that both VGCV and GCV have nearly similar efficacy in treating symptomatic CMV infected infants. Both drugs showed similar

efficacy with regards to visual function and hearing status outcome of the infants. However, VGCV seemed to produce a better effect in improving cognitive status. Moreover, VGCV had comparatively lesser side effects than GCV along with the provision for oral administration.

Abbreviations

ABR Auditory Brainstem Responses
 BAER Brainstem auditory evoked responses
 cCMV Congenital cytomegalovirus infection
 CMV Cytomegalovirus
 GCV Ganciclovir
 GDD Global developmental delay
 HI Hearing impairment
 IV intravenous
 OAE Otoacoustic emissions
 PCR Polymerase chain reaction
 qPCR Quantitative polymerase chain reaction
 SNHL Sensorineural hearing loss
 VGCV Valganciclovir

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Competing interests

The authors have declared that they have no competing interests.

Authors' contributions

All the authors contributed to data collection and also critically reviewed the manuscript. The final version of the manuscript was approved by all the authors.

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