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Valganciclovir in Infants with Hearing Loss and Clinically Inapparent Congenital Cytomegalovirus Infection: A Nonrandomized Controlled Trial

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Objective To assess the efficacy of valganciclovir in infants with hearing loss and clinically inapparent congenital cytomegalovirus infection (cCMV), as there is no consensus on treatment of this group.

Study design A nationwide, nonrandomized controlled trial, comparing 6 weeks of oral valganciclovir to no treatment in infants with cCMV, recruited after newborn hearing screening resulted in referral to an audiologist. The choice whether to treat was left to parents of subjects. Eligible subjects were full term infants aged <13 weeks with sensorineural hearing loss and diagnosed with cCMV through dried blood spot testing. The primary outcome, measured by linear and ordinal logistic regression, was change in best-ear hearing from baseline to follow-up at 18-22 months of age.

Results Thirty-seven participants were included in the final analysis, of whom 25 were in the treatment group and 12 in the control group. The majority of subjects in both groups had neuroimaging abnormalities, which were mostly mild. Hearing deterioration was more likely in the control group compared with the treatment group (common OR 0.10, 95% CI 0.02-0.45, $P = .003$). Mean best-ear hearing deteriorated by 13.7 dB in the control group, compared with improvement of 3.3 dB in the treatment group (difference 17 dB, 95% CI 2.6 – 31.4, $P = .02$).

Conclusions We investigated treatment in children with hearing loss and clinically inapparent cCMV. Although our study was nonrandomized, it is the first prospective and controlled trial in this population. Valganciclovir-treated children with hearing loss and inapparent cCMV had less hearing deterioration at 18 through 22 months of age than control subjects. *(J Pediatr 2024;268:113945)*.

EudraCT Registry number 2013-003068-30.

Congenital cytomegalovirus infection (cCMV) is the most common congenital infection worldwide and the leading cause of nongenetic sensorineural hearing loss (SNHL).[1,2] Other possible long-term sequelae include intellectual disability and neurologic, ophthalmologic, or behavioral problems. Findings such as petechiae, hepatosplenomegaly, and microcephaly are observed in approximately 15% of cases, while the majority (85%) of congenitally infected neonates appear asymptomatic at birth. About one half of symptomatic cases have long-term sequelae. However, sequelae also develop in an estimated 13.5% of the much larger group of asymptomatic neonates, who therefore account for the majority of the disease burden.[1] Without universal or targeted screening, asymptomatic cases are often diagnosed only after hearing loss is confirmed.

Despite the considerable burden of disease, there is no registered treatment for cCMV. Currently, treatment is based on 2 seminal randomized controlled trials (RCTs),[3,4] which showed that antiviral treatment initiated within the first month of life has a beneficial effect on long-term audiological and neurodevelopmental outcomes in infants with clinically symptomatic cCMV. Data from a large observational cohort have since suggested a beneficial effect in infants with cCMV and isolated

BSID-III	Bayley Scales of Infant and Toddler Development Third Edition
cCMV	Congenital cytomegalovirus infection
CONCERT	CONgenital Cytomegalovirus: Efficacy of antiviral treatment in a Randomized Trial
CONCERT 2.0	CONgenital Cytomegalovirus: Efficacy of antiviral treatment in a non-Randomized Trial with historical control group
CMV	cytomegalovirus
CNS	central nervous system
dB	Decibel
DBS	Dried blood spots
NHS	Newborn Hearing Screening
RCT	Randomized Controlled Trial
SNHL	Sensorineural Hearing Loss

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hearing loss.[5] However, as a recent systematic review on the effect of (val) ganciclovir on hearing shows, there is no evidence from prospective trials to support antiviral treatment in this latter population.[6]

The aim of the present study was to investigate whether valganciclovir treatment can prevent deterioration of hearing in children with hearing loss and clinically inapparent cCMV.

Methods

Trial Design

The original CONCERT trial (Congenital Cytomegalovirus: Efficacy of Antiviral Treatment in a Randomized Trial; EudraCT number: 2011-005378-44) was a nationwide open-label randomized controlled phase 3 trial, which began inclusion in September 2012. Data were collected and analyzed at the Leiden University Medical Center, The Netherlands. Infants were consecutively recruited through a targeted screening approach incorporated into the Newborn Hearing Screening (NHS) program. Infants who had obtained 3 subsequent "Refer" results were eligible for cytomegalovirus (CMV) PCR testing, performed on dried blood spots (DBS) collected in the first week of life by routine heel prick screening. For the DBS PCR, a whole blood spot (50 μL input volume) was used for DNA extraction. A real-time CMV PCR assay was performed in triplicate on each DBS as previously described.[7-9] If at least one in 3 replicates was positive in the initial DBS, a new DBS sample from the same patient was requested from the neonatal screening laboratory that stores the Guthrie cards. Subsequently, a confirmatory PCR was performed in triplicate on the new sample. Following written informed parental consent, CMV-positive infants were assigned in a 1:1 ratio to treatment or control group through computer-randomization by the study pharmacist. In October 2013, the randomized controlled trial (RCT) was prematurely terminated due to failed enrollment, mainly due to a lack of equipoise as both parents and pediatricians of eligible infants expressed a treatment preference. The protocol was adapted to CONCERT 2.0 (EudraCT number: 2013-003068-30), a nonrandomized trial in which the choice for treatment was left to parents. The control group was comprised of subjects who chose non-treatment as well as historical controls. The historical controls were children aged younger than 18 months with hearing loss who tested CMV positive through retrospective DBS testing. Infants diagnosed through the CONCERT procedure during the period between both studies were recruited for retrospective inclusion and constituted an interim group (**Figure 1**). Both studies were approved by the local and the national Medical Research Ethics Committees.

Study Sample

Infants eligible for trial inclusion were less than 13 weeks of age, born at term (≥37 weeks) with normal birthweight, unilateral or bilateral hearing loss (≥21 dB), diagnosed with cCMV without prior clinical suspicion and had a signed parental informed consent. For the historical control group, all children under the age of 18 months with hearing loss and newly diagnosed cCMV were eligible. Participants were excluded if signs possibly related to cCMV had been noted and medically investigated before enrollment (such as intra-uterine growth retardation, petechiae, hepatosplenomegaly, jaundice, microcephaly, thrombocytopenia, elevated transaminases, elevated bilirubin), if they were treated with other antivirals or immunoglobulins, or if they had neutropenia (<500 cells/μL or 0.5 x 10^9/L) at baseline. Signs found at inclusion for which no medical follow-up had been initiated did not result in exclusion. The same inclusion and exclusion criteria applied to the interim group, with the addition that these subjects were eligible for inclusion in the treatment group when treated for no longer than 6 weeks. We did not exclude subjects with abnormalities on neuroimaging performed after cCMV diagnosis.

Intervention

Treated infants received oral valganciclovir 16 mg/kg twice daily for 6 weeks. The dose was not adjusted for increasing weight during the treatment period. During a home visit at baseline, subjects were weighed to determine dosage and parents or legal guardians were instructed on oral administration by the researcher. The oral solutions were prepared by the pharmacist and delivered to the subject's home on the following day. If neutropenia (0.5 x 10^9/L) developed, the dose of valganciclovir was reduced by 50% or temporarily discontinued until neutrophil counts normalized. A total treatment duration of 6 weeks was planned, if blood test results and the clinical condition of the infant allowed that.

Trial Evaluations

All infants diagnosed through the CONCERT study received regular care by pediatric infectious diseases specialists, in addition to trial evaluations. During the initial home visit, medical history was taken, a physical examination was performed, including retinal examinations, and blood samples were collected for plasma CMV DNA load, complete blood count, alanine aminotransferase, aspartate aminotransferase, total bilirubin, creatinine and urea. Baseline audiologic data consisted of routine audiological assessment, which included click and/or tone burst auditory brainstem response and tympanometry. At the follow-up age of 18–22 months, an auditory brainstem response was performed by a trained investigator during a home visit or at the study site, using a Vivosonic Integrity^{tm} device (Vivosonic Inc., Canada). The study audiologist (WS), who was blinded to subject grouping, reviewed raw baseline and follow-up data and determined hearing thresholds along with the nature of hearing loss (sensorineural, conductive or mixed). Sensorineural hearing loss was defined as ≥ 21 dB perceptive unilateral or bilateral hearing loss. Hearing loss severity was classified as follows: mild 21-40 dB, moderate 41-70 dB, severe 71-90 dB, profound 91 dB or over.[10] Developmental outcome was assessed at follow-up using the Bayley Scales of Infant and Toddler Development Third Edition (BSID-III). The

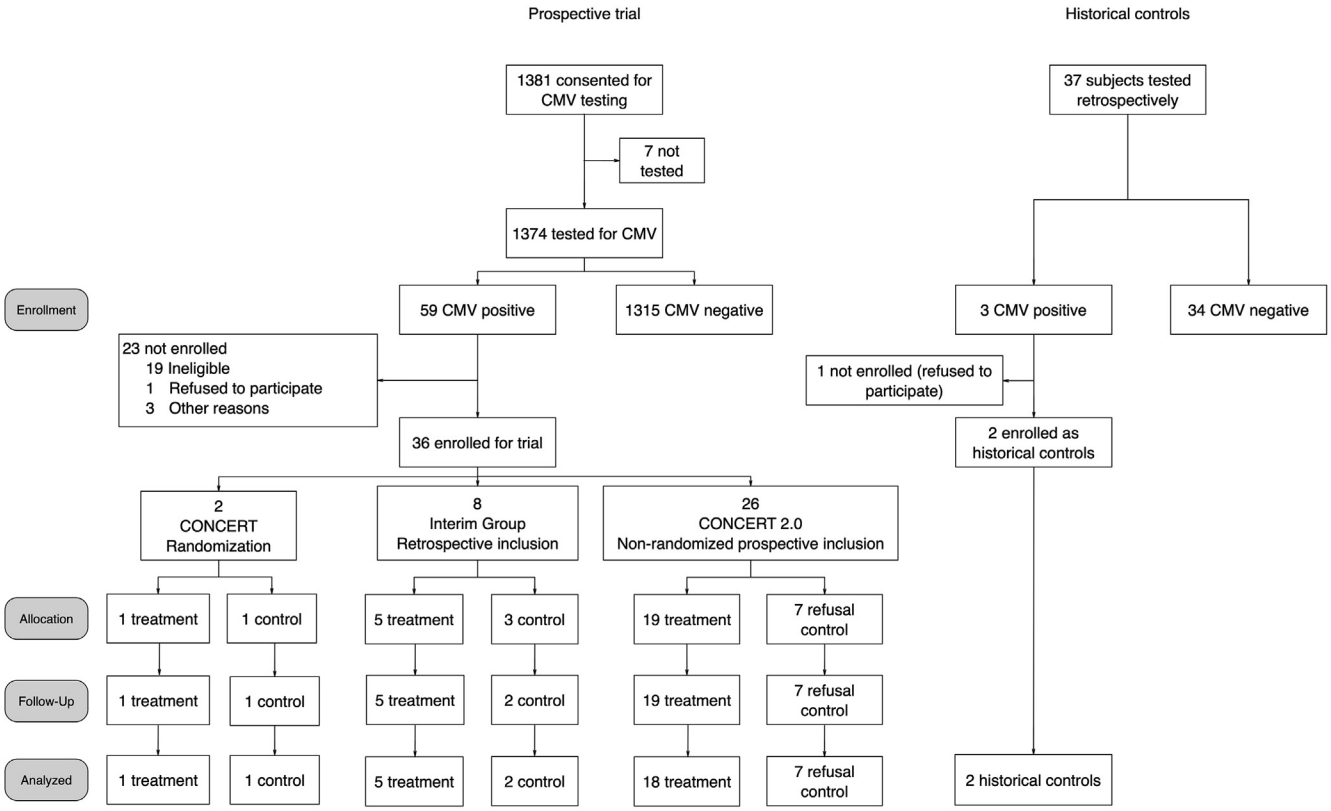

Figure 1. Randomization, Retrospective, and Prospective Inclusion of the Study Participants. Of 59 cCMV positive infants, 19 were ineligible (3 were treated for more than 6 weeks, 2 were older than 13 weeks, 7 had no confirmed SNHL, 2 were premature, 1 was small for gestational age, 2 had had signs possibly related to cCMV, 1 was already diagnosed with cCMV, and 1 subject had Down syndrome), 1 declined enrollment and 3 subjects were not enrolled due to logistical reasons. The excluded subjects that were treated for more than 6 weeks were diagnosed through the CONCERT procedure during the period between both studies. The final treatment and control groups comprise of infants recruited through several approaches. In the CONCERT trial, two patients were randomized. Eight CONCERT subjects who chose not to be randomized were retrospectively included into CONCERT 2.0 (interim group). One control subject of the interim group was lost to follow up. Numbers shown are subjects analyzed for the primary outcome. Of the prospectively included CONCERT 2.0 subjects, one subject was not evaluable in the primary outcome analysis due to unilateral otitis media at follow up. This subject was included in the total-ear hearing analyses and neurodevelopmental assessments.

tests were videotaped for evaluation by developmental psychologists who were blinded to subject grouping. The Child Development Inventory, a 300-item parent questionnaire, was administered to assess development of social, self-help, motor, language, letter and number skills, as well as the presence of behavioral problems. Parents of subjects in both study arms were instructed to keep diaries and to contact investigators if potential adverse events occurred. Plasma viral load was measured at baseline and weekly for 7 weeks in the treatment group and at baseline and week 6 in control subjects. Urine filter paper samples were collected weekly for 7 weeks and at 18–22 months for viral load measurement. No viral load assessments or diary entries were obtained from the interim group, but identical audiologic and developmental assessments were performed during the follow-up visits at 18–22 months. We requested laboratory results from treating physicians of interim group subjects to assess possible toxicity.

Outcomes

The primary outcome was the change in best-ear hearing from baseline to follow-up at 18–22 months of age. Secondary outcomes were: change in total-ear hearing from baseline to follow-up at 18–22 months; developmental outcome at 18–22 months; change in plasma and urine CMV viral load; comparison of adverse events between control and treatment groups.

Statistical Analysis

The sample size was calculated using data from Kimberlin et al.[3] We estimated that 40 participants would provide 80% power to detect a mean difference in hearing loss of 12.8 dB with standard deviations of 10.5 and 17.5 dB in the control and treated groups, respectively. Baseline characteristics of the 2 groups are reported using descriptive statistics. The statistical significance of differences was assessed by t-test or Mann–Whitney-U test for continuous variables

and chi-square or Fisher exact test for categorical variables, whereby a two-sided *P* value of less than 0.05 was considered statistically significant. For the primary and secondary hearing outcomes, we performed both best-ear and total-ear hearing analyses on continuous as well as categorized data. In the "best-ear" analysis, the better hearing ear per subject was analyzed, corresponding to a functional hearing assessment. It is possible for a subject's best hearing ear to have switched from left to right or vice versa between the 2 time points. The 'total-ear' analysis uses data from both ears as input, thus providing a biological assessment and showing the outcome of hearing loss per ear. The continuous variable of decibels hearing loss was categorized into the hearing loss severity classes as described under Evaluations. Subjects fell into 4 categories based on the change in hearing loss severity class from baseline to follow-up: 1) improved hearing, 2) maintenance of normal hearing, 3) unchanged hearing loss and 4) deteriorated hearing. A proportional odds model was performed for the categorical data analyses and continuous data were analyzed by linear regression. For total-ear analyses, the correlation between 2 ears was taken into account by performing the regression models via generalized estimating equations.

Hearing thresholds of ears with conductive loss were re-coded to 20 dB, thus treating these ears as normal hearing ears. Hearing thresholds of ears designated as having mixed hearing loss of both sensorineural and conductive nature, were analyzed as observed. In the case of cochlear implantation, we carried the last observation forward. We performed posthoc analyses excluding the interim group, adjusting for baseline hearing loss, adjusting for mixed hearing loss, excluding subjects with cochlear implants, and excluding those with severe and profound hearing loss at baseline. In some cases, retrieved raw baseline audiologic data did not reveal a specific hearing threshold as no responses were measured during ABR at the maximum sound level used. In these cases, we re-coded the value as the maximum sound level plus 10 dB. For instance, if no peak V was registered at 100 dB, a threshold of 110 dB was noted. Developmental outcomes were compared per domain using t-tests and Chi-square or Fisher exact test. Differences between and within groups in mean viral load and their course over time were studied and tested for significance using t-tests or paired t-tests. All analyses were performed using IBM SPSS Statistics for Windows, Version 25.0. (Armonk, NY: IBM Corp).

Results

Between September 2012 and December 2016, 1,381 infants were enrolled for CMV testing on DBS. Of these, 1374 (99%) were successfully tested (**Figure 1**). Fifty-nine (4.3%) infants tested positive for CMV. Twenty-three cCMV positive subjects were not enrolled in the trial. Of these, 19 were ineligible (7 met exclusion criteria, 12 did not meet inclusion criteria), 1 declined enrollment and 3 subjects were not enrolled due to logistical reasons. Details are described in **Figure 1**. Thirty-six infants participated in the trial, of whom the first 2 were randomized. One subject was lost to follow-up. After retrospectively testing an additional 37 infants with hearing loss, 2 subjects were included as historical controls. In total, 25 infants were treated and 12 infants were included in the combined refusal and historical control group. Baseline demographic and clinical characteristics are shown in **Table I**. Five children (3 in the control group, 2 in the treatment group) had a unilateral cochlear implant at follow-up, and one had bilateral implants (treatment group). Six of these 7 impaired ears had profound hearing loss at baseline, and one had severe hearing loss.

Primary Outcome

One treated subject could not be assessed in the best-ear analyses due to unilateral otitis media with effusion at follow-up. Of the remaining 24 subjects in the treatment group, the best-ear hearing category improved from baseline to follow-up in 3 subjects (13%), remained normal in 12 (50%), was unchanged in 7 (29%) and deteriorated in 2 (8%). In the control group, none improved, 2 subjects (17%) maintained normal hearing, 4 (33%) had unchanged hearing loss and 6 (50%) had deteriorated hearing (**Table II**; $P = .003$). On average, hearing deteriorated by 13.7 dB in the control group while the treated group showed a mean improvement of 3.3 dB (**Table III**; difference 17 dB, 95% CI 2.6 to 31.4, $P = .020$). Two of 4 control subjects and none of the 12 treated subjects with unilateral hearing loss at baseline progressed to bilateral hearing loss at follow-up. **Figures 2** A and B show a graphic representation of the hearing courses of the best hearing ears.

Secondary Outcomes

The total-ear hearing analyses showed results similar to the best-ear analyses, with control ears showing more deterioration than treated ears (**Table II** and **III**, **Figures 2** C and D). No significant differences in any developmental domain were found between treatment and control groups (**Table IV** and **Table V**). The mean viral load in plasma decreased in both groups. In the treatment group, the mean plasma viral load decreased significantly from baseline to 6 weeks ($P < .0001$) and was significantly lower at 6 weeks compared with the control group ($P = .006$). However, the change in mean plasma viral load from baseline to 6 weeks did not differ significantly between the groups ($P = .34$). The mean viral load in urine showed a significantly greater decline from baseline to 6 weeks in the treatment group compared with the control group, but the mean load converges to the same level in both groups at the 18-22 month follow-up (**Figure 3**). There was one serious adverse event: a treated infant was hospitalized for 2 nights for observation due to a brief, resolved unexplained event. The event was rated as unlikely to be related to the study drug by the treating pediatrician. One subject discontinued treatment temporarily due to anemia 7.09 g/dL (Hb 4.4 mmol/L),

Table I. Baseline characteristics

Baseline characteristic*	Control (n = 12)	Treatment (n = 25)	*P* Value
Age in weeks at start of treatment, median (IQR)	NA	8 (6–10.5)	NA
Age in days at start of treatment, median (range)	NA	61 (19–88)	NA
Gestational age in weeks, mean (SD)	38.9 (1.1)	39.5 (1.3)	.16
Birth weight in g, mean (SD)	3107 (530)	3220 (470)	.52
Sex (% female)	58	52	.71
Head circumference, mean SD	−1.05	−0.41	.10
Microcephaly†	2 (17)	2 (8)	.43
Cerebral ultrasound	8 (67)	21 (84)	.39
Abnormalities on cerebral ultrasound‡	8 (100)	19 (90)	1
Maternal educational attainment			
Secondary education	1 (8)	3 (12)	.95
Secondary vocational education	5 (42)	7 (28)	
Higher vocational education	2 (17)	8 (32)	
Academic education	4 (33)	7 (28)	
Unilateral or bilateral hearing loss at baseline			
Unilateral	4 (33)	13 (52)	.32
Bilateral	8 (67)	12 (48)	
Best ear hearing at baseline			
Normal	4 (33)	13 (52)	.51
Mild HL	3 (25)	3 (12)	
Moderate HL	4 (33)	4 (16)	
Severe HL	0	2 (8)	
Profound HL	1 (8)	3 (12)	
Total ear hearing at baseline	n = 24 ears	n = 50 ears	
Normal	4 (17)	13 (26)	.1
Mild HL	3 (12)	3 (6)	
Moderate HL	7 (29)	6 (12)	
Severe HL	6 (25)	8 (16)	
Profound HL	4 (17)	20 (40)	

cUS, cranial ultrasound; *HL*, hearing loss; *IQR*, interquartile range; *MRI*, magnetic resonance imaging; *NA*, not applicable; *SD*, standard deviation.
*Data are n (%) unless stated otherwise.
†Microcephaly definition: more than 2 standard deviations below average.
‡Abnormalities on cerebral ultrasound (n): control group: single lenticulostriate vasculopathy (2); germinolytic cysts (1); mild ventriculomegaly (1); lenticulostriate vasculopathy and germinolytic cysts (2); lenticulostriate vasculopathy and mild ventriculomegaly (1); extensive lenticulostriate vasculopathy (1); treatment group: single lenticulostriate vasculopathy (7); germinolytic cysts (4); mild ventriculomegaly (2); single calcifications (1), germinolytic cysts and mild ventriculomegaly (1); lenticulostriate vasculopathy and germinolytic cysts (2); lenticulostriate vasculopathy, germinolytic cysts and single calcifications (1); lenticulostriate vasculopathy, mild ventriculomegaly, extensive calcifications, atrophy, suspected migrational disorder and dysgenesis of corpus callosum (1).

mild leukopenia 4140 cells/μL (4.14 x 10^9/L) and neutropenia 820 neutrophils/μL (0.82 x 10^9/L), which resolved 3 days after discontinuation of the drug. Another subject stopped treatment for a week because of gastrointestinal complaints that subsequently were not attributed to valganciclovir. Laboratory results were available for all prospectively included subjects. Three of the 20 treatment subjects developed neutropenia: one resolved spontaneously without dose change, one required temporary drug discontinuation and one subject received half doses for 3 days. In the control group, 1 of 8 subjects had neutropenia. All treated participants completed a total of 6 weeks of valganciclovir and none of the controls received valganciclovir.

Table II. Audiological outcome, categorical data analysis

Analysis	Best-ear		Total-ear	
Group	Control	Treatment	Control	Treatment
Number of participants or ears	12	24	24	49
Improved at follow-up	0	3 (13)	1 (4)	6 (12)
Normal hearing at baseline and follow-up	2 (17)	12 (50)	2 (8)	13 (27)
Same hearing loss at baseline and follow-up	4 (33)	7 (29)	11 (46)	26 (53)
Deteriorated hearing at follow-up	6 (50)	2 (8)	10 (42)	4 (8)
Common OR (95%CI)*	0.10 (0.02-0.45)		0.16 (0.05-0.47)	
P value	0.003		0.001	

Data are n (%) unless stated otherwise.
*Best ear analysis: proportional odds model, total ear analysis: proportional odds model, via General Estimating Equations.

Ancillary Analyses

Posthoc analyses as described in Methods, performed to test the robustness of the findings had no impact on the observed effect in the primary outcome analyses.

Table III. Audiological outcome, continuous data analysis

Analysis	Best-ear		Total-ear	
Group	Control	Treatment	Control	Treatment
Number of participants or ears	12	24	24	49
Change in dB HL threshold (dB)	13.7	−3.3	13.9	−1.3
Difference (95% CI)	17 (2.6–31.4)		15.2 (4.2–26.1)	
P value*	0.02		0.007	

dB HL, decibels Hearing Level; *dB*, decibel.
Data are n (%) unless stated otherwise.
*Best ear analysis: linear regression, total ear analysis: linear regression, via General Estimating Equations.

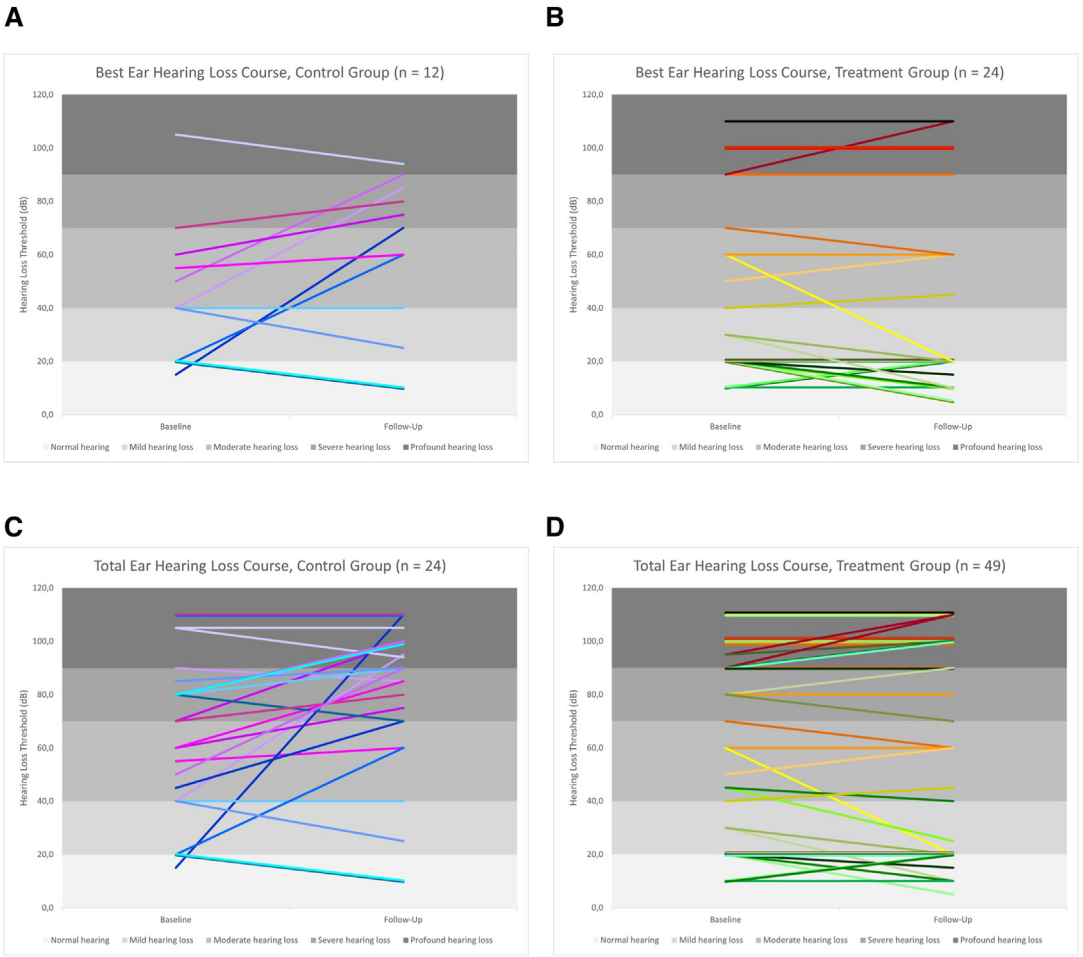

Figure 2. Hearing Loss Course from Baseline to Follow-Up at 18-22 Months. dB, decibels. Each unique color represents an individual subject. Panel A shows hearing loss courses of the best hearing ear (best-ear) per subject at 2 timepoints for the control group and panel B shows best-ear hearing for the treatment group. Panel C shows hearing loss courses of each ear (total-ear) for the control group and panel D shows total-ear hearing for the treatment group.

Discussion

In this nationwide controlled trial, children who received 6 weeks of valganciclovir started in the first 3 months of life showed less deterioration of hearing than control subjects.

Our study sample is relevant as NHS-driven targeted cCMV screening is being advised and implemented in an increasing number of countries.[11] The indication for treatment is clear in neonates with clinically apparent disease and central nervous system (CNS) involvement [3,4,6] and there is consensus that asymptomatic infants should not be treated.[6,12] Our study is the first prospective controlled treatment trial in infants with hearing loss and otherwise clinically inapparent cCMV. While RCTs provide the best possible evidence of efficacy, randomization has proven to be challenging in this patient population, as evidenced by our effort and the ValEAR trial, which recently was halted prematurely due to enrollment difficulties (Albert H. Park, M.D., University of Utah, Salt Lake City, personal communication). Therefore, we believe that data from our nonrandomized trial provide important evidence on treatment effect in children with hearing loss and clinically inapparent cCMV. Of note, the ValEAR trial was a double-blinded trial investigating asymptomatic cCMV infected hearing-impaired infants, with elaborate exclusion

Table IV. Developmental outcome (BSID-III)

BSID-III component	Control, n = 12 (mean ± SD)	Treatment, n = 25 (mean ± SD)	*P* Value
Cognitive composite score	95.5 ± 10.2	97.0 ± 17.0	.79
Language composite score	74.6 ± 13.1	83.2 ± 16.4	.12
Expressive scaled score	6.6 ± 3.2	8.0 ± 3.2	.22
Receptive scaled score	4.0 ± 2.3	5.7 ± 3.9	.16
Motor composite score	96.2 ± 9.4	96.6 ± 18	.93
Fine motor scaled score	11.7 ± 1.7	10.6 ± 3.4	.33
Gross motor scaled score	6.8 ± 2.8	7.8 ± 3.2	.34

BSID-III, Bayley Scales of Infant and Toddler Development Third Edition.

Table V. Delay in developmental outcome (CDI)

Delay in CDI component	Control, n = 10	Treatment, n = 23	*P* Value	Total delayed, n = 33
Social	0	2 (8.7)	.74	2 (6.1)
Self-help	0	5 (21.7)	.25	5 (15.2)
Gross motor	4 (40)	5 (21.7)	.40	9 (27.3)
Fine motor	0	3 (13.0)	.52	3 (9.1)
Language production	1 (10)	6 (26.1)	.40	7 (21.2)
Language receptive	4 (40)	5 (21.7)	.40	9 (27.3)
Letters	0	0		0
Numbers	0	0		0
General development	0	2 (8.7)	.74	2 (6.1)

CDI, Child Development Inventory.
Data are n (%).
Delay is defined as <-2 SD.

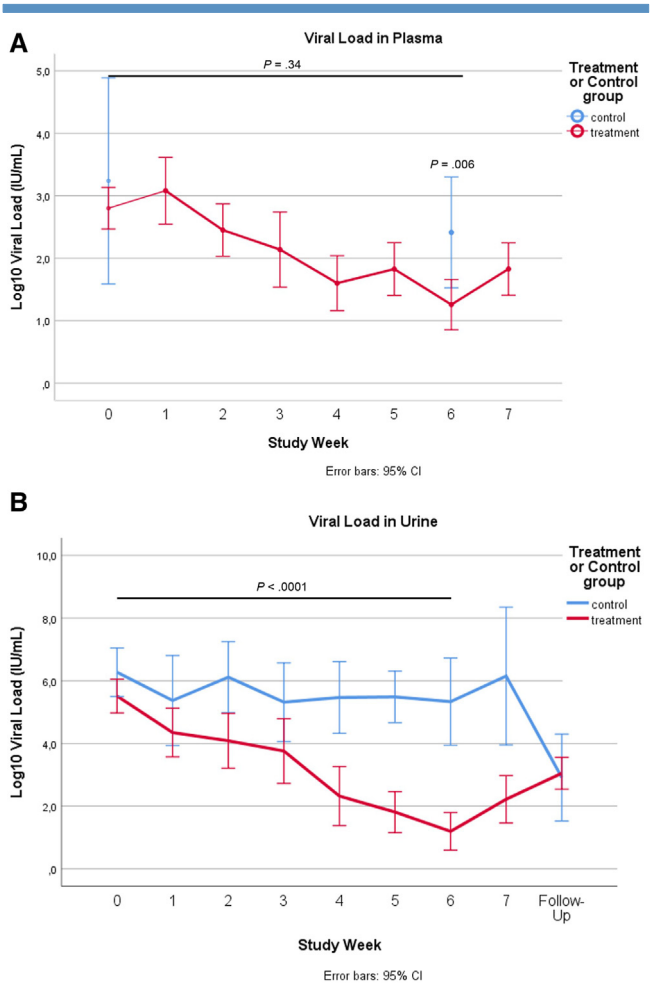

Figure 3. Cytomegalovirus DNA Load in Plasma and Urine. A. The mean viral load (IU/mL) in plasma of treatment and control subjects. Control subjects were tested at baseline and after 6 weeks. B. The mean viral load (IU/mL) in urine of treatment and control subjects. Follow-up age was 18-22 months.

criteria such as evidence of intracranial calcifications or hydrocephalus.

In the absence of universal screening, there is often a delay in diagnosing infants with cCMV. However, prospective data on treatment initiation beyond the neonatal period are scarce. In the only 2 RCTs on cCMV management, treatment was started within the first month of life.[3,4] Retrospective uncontrolled studies have suggested that treatment started beyond the neonatal period[13-15] may be of therapeutic benefit and a recent prospective uncontrolled trial showed no difference in audiologic outcome between infants who started treatment before 1 month and those who started up to the age of 2 months.[16] Our study shows that therapy started within the first 3 months of life can be beneficial. Valuable prospective data on this matter were generated concurrently to our trial, when Kimberlin et al conducted an RCT in which they studied 6 weeks of valganciclovir treatment, started between 1 month and 4 years of age.[17] They found no evidence of an effect on hearing in their combined symptomatic and asymptomatic sample compared with an untreated control group. Stratifying for symptomology or age at enrollment did not affect this finding (David W. Kimberlin, M.D., University of Alabama, Birmingham, personal communication). This is an indication that there is a limited window of opportunity for benefit from antiviral treatment.

Treatment duration also remains an important and controversial issue. The evidence for a 6-week treatment course was generated by the first and only placebo-controlled RCT in 2003, which showed a benefit of treatment with intravenous ganciclovir in symptomatic children with CNS involvement.[3] Because a subsequent RCT reported a modest benefit of 6 months of valganciclovir compared with a 6-week course after adjusting for CNS involvement at baseline, a 6-month regimen currently is used widely.[4,12] Regarding the choice of a 6-week regimen in the CONCERT study, it is important to note that the trial began before the publication of the aforementioned CASG study.[4] Furthermore, there was no evidence of any treatment benefit in the non-comparable sample of less severely affected cases studied in the CONCERT study. To determine the optimal treatment duration, more research comparing efficacy of different regimens is needed.

In addition to the evidence for 6 months of treatment in a symptomatic population provided by the RCT by Kimberlin et al, there are scarce data on long-term treatment, especially in a cohort similar to ours. The Schneider Children's Medical Center of Israel study group has published multiple analyses of the effects of a 1-year antiviral treatment regimen in their large cohort of children with cCMV, including an analysis of children with isolated hearing loss. They report remarkably high rates of improved hearing and return to normal hearing.[5,14,15,18,19] However, the cohort includes a significant proportion (around 40%) of subjects born following primary maternal infection in the second or third trimester. This is noteworthy, since the presence of SNHL is expected to result mostly from vertical CMV transmission during the first trimester of pregnancy.[20-24] Furthermore, these retrospective cohort studies are uncontrolled.

When we consider the possible mechanisms of CMV-induced hearing loss, long-term antiviral treatment would be sensible if it were caused by ongoing viral replication in the inner ear. Although CMV DNA has been found in the inner ear years after birth,[25-29] it is unknown whether this represents viral replication. Since peripheral immunologic viral control is expected to develop in congenitally infected infants, it may also occur in the inner ear, as this is not an immune-privileged site.[30,31] Our viral load data indicate a role for natural peripheral immunity as the mean viral load decreases in both control and treatment groups.[32] Possible neuropathologic mechanisms other than direct viral effects, such as CMV-induced inflammation or ongoing ion-disbalance in the inner ear, have been suggested as important pathologic pathways in both animal models and human histopathologic studies, and could explain progressive hearing deterioration.[30,31,33]

There are several limitations of our study, the most fundamental of which is the failure to achieve randomization and the necessary change in trial design, resulting in treatment groups with participants recruited via different approaches. While this presented organizational challenges and delayed our analyses, it should not have affected the primary endpoint as we performed the same objective follow-up assessments in each patient. There were no significant differences between groups at baseline, although the groups are small and the possibility of residual confounding remains. We found no significant treatment effect on neurodevelopmental outcomes. As our sample size calculation was based on the primary outcome, the study may have been underpowered to detect significant differences. It is important to note that the receptive and expressive language scores in the BSID-III may be underestimated because the test was performed in spoken Dutch and was not supported by sign language. This applies to both study groups. Missing diary entries and serial viral loads of the interim group may have resulted in information bias. Valganciclovir was generally well tolerated, with reversible neutropenia in 15% of treated vs 12,5% of control cases. Finally, prospective and systematic recording of clinical and neuroimaging data directly after cCMV diagnosis would have resulted in more homogeneous and complete data.

The CONCERT study was designed to identify otherwise undiagnosed infants with cCMV and isolated hearing loss, excluding those with clinically apparent symptoms and signs. Our trial sample is of interest because it represents a highly clinically relevant group of children diagnosed today, in the absence of screening. Moreover, the CONCERT sample is complementary to the samples described in the previously published RCTs.[3,4] It is important to note that neuroimaging abnormalities were found in the vast majority of both control and treatment groups. Using the Alarcon score, these were mostly categorized as mild.[9,34] Therefore, the CONCERT sample is best not described as "asymptomatic with isolated hearing loss". The prognostic importance of mild abnormalities is not yet established, and whether they constitute a treatment indication is still a subject of discussion.[12,35,36] Other studies describing small cohorts of children detected through targeted hearing-based screening show that imaging abnormalities are not uncommon in this group.[9,37-41] Since our trial sample is unselected regarding these mild abnormalities, we consider the results to be generalizable when applied to infants detected by targeted hearing-based screening.

While uncertainties remain about the precise conditions under which benefits of valganciclovir can be expected in children with cCMV, our findings narrow knowledge gaps regarding indication, age at initiation and duration of treatment. The data from this prospective controlled trial show that 6 weeks of valganciclovir, initiated in the first 3 months of life, has a beneficial effect on hearing outcome in children with hearing loss and clinically inapparent cCMV. This finding has profound implications for health policy and patient care, justifying the implementation of targeted hearing-based cCMV screening, and aiding the clinician in the management of infants diagnosed with hearing loss and clinically inapparent cCMV.■

CRediT Authorship Contribution Statement

Pui Khi Chung: Data curation, Formal analysis, Methodology, Visualization, Writing – original draft. **Fleurtje A.J. Schornagel:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Wim Soede:** Investigation, Writing – review & editing. **Erik W. van Zwet:** Formal analysis, Methodology, Writing – review & editing. **Aloys C.M. Kroes:** Supervision, Writing – review & editing. **Anne Marie Oudesluys-Murphy:** Conceptualization, Funding acquisition, Methodology, Supervision, Writing – review & editing. **Ann C.T.M. Vossen:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

Declaration of Competing Interest

A.C.T.M.V. reports financial support was provided by NutsOhra Fund (grant number 0901-054). A.M.O.-M. reports a relationship with National advisory board on newborn hearing screening that includes board membership. The other authors declare no conflicts of interest.

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Data Statement

Data sharing statement available at www.jpeds.com.

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