The Effect of (Val)ganciclovir on Hearing in Congenital Cytomegalovirus: A Systematic Review

Elise De Cuyper, MD ©; Frederic Acke, MD, PhD ©; Annelies Keymeulen, MD ©; Ingeborg Dhooge, MD, PhD ©

**Objective:** To search for existing evidence of a beneficial effect of (val)ganciclovir on hearing in children with congenital cytomegalovirus (cCMV) infection and to identify future research questions.

**Study Design:** Systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, searches were performed in PUBMED, EMBASE, and WEB OF SCIENCE on December 15, 2021.

**Methods:** Studies providing ear-specific hearing results after treating children with cCMV-related hearing loss with (val)ganciclovir were retained. A meta-analysis [Peto odds ratio (OR), Review Manager 5.3] was performed to compare hearing outcome between treated and untreated children. The National Institutes of Health tool was used for quality assessment and heterogeneity was assessed with $I^2$ statistics.

**Results:** Eighteen studies with a total of 682 treated patients were included for the systematic review. Our meta-analysis showed that treating symptomatic children with hearing loss resulted in more hearing improvement [Peto OR 7.72, 95% confidence interval (CI) 3.08–19.34] and less hearing deterioration [Peto OR 0.23, 95% CI 0.10–0.57]. Relative to an improvement and deterioration rate of 9.4% and 28.2% in an untreated group, the rate of the treated group was 44.5% and 6.3%, respectively.

**Conclusions:** There is sufficient evidence in literature to support treatment with (val)ganciclovir of children with symptomatic cCMV and hearing loss. However, still today, there is insufficient evidence of the potential beneficial role of (val)ganciclovir on hearing outcome of children with isolated hearing loss, late-onset hearing loss, and asymptomatic cCMV. The urgent need for future prospective, randomized clinical trials still exists. A standardization of definitions and treatment protocols would create uniformity in future studies.

**Key Words:** Congenital cytomegalovirus, hearing loss, treatment, ganciclovir, valganciclovir.

**INTRODUCTION**

With a reported prevalence of 7 per 1,000 births, congenital cytomegalovirus (cCMV) infection is the most frequent congenital infection worldwide and the major cause of congenital nonhereditary sensorineural hearing loss (SNHL) in industrialized countries.1–3

Ten to 15% of children with cCMV are symptomatic at birth.1,2 Outcome for these infants is poor, most survivors suffer from severe neurologic sequelae and half of the children will develop some degree of hearing loss.2,3 The majority of children with cCMV will have no clinical apparent signs or symptoms of disease at birth (asymptomatic cCMV). However, approximately 10–15% of them will develop some degree of late-onset hearing loss.2,4,5

Increased awareness among health care workers has led to increased prenatal screening for maternal seroconversion. Newborns are increasingly tested for cCMV when abnormalities are detected during routine ultrasonography or maternal serology.7 Furthermore, screening for cCMV is part of the diagnostic work up in newborns with a failed neonatal hearing screening in Belgium.8 Because of earlier diagnosis and a more thorough medical evaluation, babies with cCMV now presenting to pediatricians differ from those primarily included in clinical trials reported in the literature.7,8 This has led to a change in definition of cCMV infected children.8 Until recently children were categorized as symptomatic (having apparent clinical signs or symptoms at birth) or asymptomatic.9

Based on the increased awareness, increased detection of cCMV neonates and the more thorough diagnostic investigations, the International Expert Consensus Statement on Diagnosis and Management of cCMV published in 2017 actually suggests four categories: 1) moderately to severely symptomatic cCMV, 2) mildly symptomatic cCMV, 3) asymptomatic cCMV with isolated SNHL, and 4) asymptomatic cCMV.10 A detailed description of each category can be found in the article of Rawlinson et al. (panel 2).10 Also in 2017, a guideline suggested by a European Expert Consensus Statement on Diagnosis and Management divided children into slightly different categories (mildly symptomatic cCMV—moderately symptomatic cCMV—severely symptomatic cCMV—asymptomatic cCMV).11
Both drugs induce antiviral effects by inhibition of the CMV polymerase.11 Today, in most centers valganciclovir is offered to children with symptomatic cCMV. The decision is made after a balanced deliberation of short and long-term risks and potential benefits and in consultation with the parents.9 Neutropenia and thrombocytopenia are the most important side effects and may require a dose adjustment or temporary cessation of therapy.1,11–13

The International Expert Consensus Statement on Diagnosis and Management of cCMV suggests guidelines for treatment based on current evidence from the literature.10 As a beneficial effect of treatment on neurodevelopmental outcome has been demonstrated in moderately to severely symptomatic children, they recommend treating those children within the first month of life with oral valganciclovir 16 mg/kg per dose twice a day for a maximum duration of 6 months. Antiviral therapy for children with isolated SNHL is not routinely recommended as sufficient evidence is lacking. Antiviral treatment in asymptomatic children, even though they are at risk for delayed-onset hearing loss, is also not recommended.7,10 Moreover, evidence from randomized trials to initiate antiviral therapy beyond the first month of life is absent.10 However, these guidelines are not universally applied.

Despite the significant long-term impact of cCMV infection, no standardized therapeutic approach for cCMV-related hearing loss exists.10 This systematic review was conducted to analyze existing evidence for the beneficial effect of treatment on hearing outcome and to identify future research questions.

METHODS

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria.14 Searches in PUBMED, EMBASE, and WEB OF SCIENCE were performed on December 15, 2021. Inclusion was based on the acronym PICO, where patients were children with (a risk of) cCMV-related hearing loss, intervention was treatment with (val)ganciclovir, control was no treatment, and outcome was ear-specific hearing results. A search strategy was developed using The National Library of Medicine’s Medical Subject Heading (MeSH) browsers to identify MeSH indexed terms. Following algorithms were used in PUBMED (1), EMBASE (2), and WEB OF SCIENCE (3), respectively: 1) cytomegalovirus infections (MeSH Terms!) and (hearing loss [MeSH Terms]), 2) ‘cytomegalovirus infection’ and ‘hearing impairment’, and 3) (cytomegalovirus infections) and (hearing loss); no publication date was imposed. The first screening based on title and abstract aimed at the inclusion of articles investigating the effect of ganciclovir/valganciclovir (given intravenously or orally) on hearing outcome in human cCMV. Studies analyzing the effect of hyperimmunoglobulin therapy were not included. Case reports, reviews, and conference abstracts were excluded as well as non-English articles. After the second screening based on full text, only studies providing an ear-specific analysis with audiological testing before treatment initiation and detailed audiological follow-up thereafter were retained. Exclusion criteria were no link between hearing loss and therapy, review, no adequate audiological follow-up, and no ear-specific analysis. In case of studies with overlapping study populations, only the most informative study was considered eligible. The process as described above was completed by two authors independently; mutual agreement could be reached after a thorough discussion. Both studies using a control group and before–after studies to investigate the effect of (val)ganciclovir on hearing outcome in children with cCMV were eligible. In this systematic review, the definitions for symptomatic cCMV and hearing improvement defined by the original author of the paper are used though discrepancies are present.

Quality assessment was performed by two authors (EDC and FA) independently using the National Institutes of Health (NIH) tool. Based on the design of the study, the NIH tool for observational cohort and cross-sectional studies, controlled intervention studies, or case series studies was included.15 In order to process all data objectively, a data-extraction sheet was developed and approved by all authors. Information about the study (design, country, sample size, etc.), characteristics of the participants, type of intervention (dose, duration, frequency, etc.), and details about the outcome were collected. In order to differentiate between a case series and a cohort study, comparison of hearing outcome between different treatment protocols was considered a cohort study. Some minor changes were made after pilot-testing on five articles. One author (EDC) extracted all data and a second author (FA) checked it by random sampling.

Subsequently, a meta-analysis was performed to compare treated and untreated children for hearing improvement as well as for hearing deterioration. All the subgroups of cCMV were included. An individual study was retained if the following conditions were fulfilled: 1) hearing evolution (stable/hearing improvement/hearing deterioration) was reported as a per ear analysis, 2) hearing evolution is known for the majority of the ears, and 3) the study reported hearing evolution for both treated and untreated ears. Moreover, concerning the analysis for hearing improvement, only ears with hearing loss at birth were included. Review Manager 5.3 was used to perform a fixed-effects model based on the Peto method to calculate odds ratio (OR) and 95% confidence interval (CI).16 Findings are represented by forest plots. The assumed percentage of hearing improvement and hearing deterioration for treated children was calculated

\[
p_{\text{treatment}} = \frac{1}{\text{OR} \times p_{\text{control}} + \text{OR} - 1} + p_{\text{control}}
\]

To assess heterogeneity among the studies, \( I^2 \) test statistic was utilized.

RESULTS

Search Process

The computerized searches resulted in 436 articles in PUBMED, 736 articles in EMBASE, and 967 articles in WEB OF SCIENCE. By manually searching citations, personal libraries, and reference lists of the retrieved articles, three additional records were added. Of the 2139 articles, 979 were removed as being duplicates. A total of 1,160 records were screened based on title and abstract. A total of 1,135 records were excluded and 25 articles were assessed for eligibility by reading their full text, added with the 3 articles found by manual search. Finally, 18 articles published between 2003 and 2020 were selected to be included in this systematic review.
consisting of nine case series, five retrospective cohort studies, two prospective cohort studies, and two randomized controlled trials (Figure 1). The NIH quality assessment and data-extraction sheet are represented by Supporting Tables 1 and 2. The quality of the included studies varied. Only two randomized prospective clinical trials were included.

**Subjects**

The 18 criteria-meeting studies included a total of 682 treated patients. All investigations were conducted in a tertiary center; the majority of the studies were monocentric (14/18). The studies were performed in Israel (n = 6), Japan (n = 3), United States (n = 3), Belgium (n = 2), Italy (n = 2), Spain (n = 1), and Austria (n = 1). The number of treated children ranged between 6 and 149 per study (Table I). Of the 18 included studies, only 7 reported results of a comparator group of untreated children ranging from 6 to 90 children. Median time of follow-up was reported by 11 researchers, which was on average 45.5 months (range 6 months until 10 years). An overview of the definition for symptomatic cCMV used by each author is represented in Supporting Table 3. Late-onset hearing loss is defined as normal hearing at birth followed by hearing loss. The proportion of treated children in this review is as follows: 497 symptomatic cCMV, 36 asymptomatic cCMV, 77 isolated hearing loss at birth, and 46 late-onset hearing loss. A total of 26 children could not be grouped as these categories were not clearly defined by one author.

Of the seven studies reporting results of a comparator group of untreated children, four studies were excluded for the analysis of hearing improvement and three studies were excluded for the analysis of hearing deterioration in view of the meta-analysis. Ears with hearing loss at birth and ears without hearing loss at birth were analyzed separately. Hearing improvement and hearing deterioration were compared between 61 treated ears and 61 untreated ears with hearing loss at birth (children with symptomatic cCMV, asymptomatic cCMV, or isolated hearing loss). Hearing deterioration for children without hearing loss at birth was compared between 41 treated and 39 untreated ears (children with symptomatic or asymptomatic cCMV).

**Treatment**

Most of the children were treated based on central nervous system (CNS) involvement. Four studies included children with isolated hearing loss at birth, two studies focused on asymptomatic children, and another two studies investigated treating children with late-onset hearing loss. All the children with late-onset hearing loss were asymptomatic with normal hearing at birth; audiological follow-up revealed late-onset hearing loss. Therapy consisted of intravenous ganciclovir, oral ganciclovir, oral valganciclovir, or a combination. No children received steroids for sudden onset SNHL. For the 18 studies,
11 different treatment protocols are described (Supporting Table 3). Overall, ganciclovir has been assessed in five studies, valganciclovir in four studies, and a combination therapy in nine studies. Due to new insights, treatment protocols could have changed during the study period. Treatment duration ranged from 5 weeks to 12 months.

### Hearing Assessment

In order to assess hearing status, 17 studies used Brainstem Evoked Response Audiometry, 10 studies performed behavioral hearing tests (visual reinforcement audiometry, conditioned play audiometry, or conventional audiometry), 3 studies tested otoacoustic emissions and 2 used Auditory Steady-State Responses. Tympanometry was routinely performed in six studies to rule out middle ear pathology, in two studies it was only performed in case of suspected conductive hearing loss. Definition and categorization of hearing loss differed between studies as well as the definition of hearing improvement (Supporting Table 4). Some authors applied 10 dB as cut-off value for a significant change in hearing status while others also required a change in hearing category (mild/moderate/severe/profound) or recognized changes in the auditory threshold only from a difference of 15 to 20 dB between two-time points.

### Posttreatment Hearing Outcome

Reported outcome is divided into three categories as described in the individual studies: improved, stable, and deteriorated hearing. Stable hearing may include both children who maintained normal hearing and children with stable hearing impairment since birth. Table II gives an overview of the posttreatment hearing outcome of the 18 included articles. If children were evaluated at different moments in time, only the results of the last follow-up are represented. The percentage of improved, stable, and deteriorated hearing ranged from 12.5% to 82.9%, 7.1% to 100.0%, and 0.0% to 35.3%, respectively. Among the 18 included studies, 7 studies reported hearing improvement in more than half of the treated ears.

### TABLE I.

Characteristics of the Included Studies.

<table>
<thead>
<tr>
<th>First Author (Reference)</th>
<th>Design</th>
<th>Treatment Group</th>
<th>Route of Administration</th>
<th>Onset of Therapy</th>
<th>N Treated/Untreated Children</th>
<th>Median Time of Follow-up (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amir17</td>
<td>2</td>
<td>Late-onset hearing loss</td>
<td>IV or oral</td>
<td>Age of 4–34 mo</td>
<td>21/0</td>
<td>34</td>
</tr>
<tr>
<td>Amir18</td>
<td>1</td>
<td>Symptomatic cCMV</td>
<td>IV and oral</td>
<td>Neonatal period.</td>
<td>23/0</td>
<td>/</td>
</tr>
<tr>
<td>Bilavsky19</td>
<td>2</td>
<td>Symptomatic cCMV</td>
<td>IV or oral</td>
<td>At birth.</td>
<td>76/65</td>
<td>/</td>
</tr>
<tr>
<td>Bilavsky20</td>
<td>2</td>
<td>Symptomatic cCMV</td>
<td>IV or oral</td>
<td>During the first 4 wk of life.</td>
<td>149/0</td>
<td>40.2</td>
</tr>
<tr>
<td>del Rosal21</td>
<td>2</td>
<td>Symptomatic cCMV</td>
<td>IV or oral</td>
<td>Age of 1.8–8.8 mo</td>
<td>13/0</td>
<td>/</td>
</tr>
<tr>
<td>Dorfman22</td>
<td>2</td>
<td>1) Symptomatic cCMV 2) Late-onset hearing loss</td>
<td>IV or oral</td>
<td>Age of 12–156 wk</td>
<td>91/0</td>
<td>44.1 (symptomatic cCMV) 57.3 (asymptomatic cCMV)</td>
</tr>
<tr>
<td>Foulon23</td>
<td>3</td>
<td>1) Symptomatic cCMV 2) Isolated hearing loss</td>
<td>IV</td>
<td>At birth.</td>
<td>6/62</td>
<td>45</td>
</tr>
<tr>
<td>Kimberlin24</td>
<td>4</td>
<td>Symptomatic cCMV</td>
<td>IV</td>
<td>Neonatal period.</td>
<td>24/18</td>
<td>21.9</td>
</tr>
<tr>
<td>Kimberlin25</td>
<td>4</td>
<td>Symptomatic cCMV</td>
<td>Oral</td>
<td>Neonatal period.</td>
<td>86/0</td>
<td>/</td>
</tr>
<tr>
<td>Koyano26</td>
<td>2</td>
<td>Isolated hearing loss</td>
<td>IV or oral</td>
<td>Neonatal period.</td>
<td>10/50</td>
<td>36 (mean)</td>
</tr>
<tr>
<td>Lackner27</td>
<td>2</td>
<td>Asymptomatic cCMV</td>
<td>IV</td>
<td>Within the first 10 d of life.</td>
<td>12/11</td>
<td>70.8</td>
</tr>
<tr>
<td>Mazzaferri28</td>
<td>2</td>
<td>Isolated hearing loss</td>
<td>IV or oral</td>
<td>Within the first 10 d of life.</td>
<td>7/6</td>
<td>/</td>
</tr>
<tr>
<td>Michaels29</td>
<td>2</td>
<td>Symptomatic cCMV</td>
<td>IV and oral</td>
<td>Age of 3 d to 11 mo.</td>
<td>9/0</td>
<td>24</td>
</tr>
<tr>
<td>Ohyama30</td>
<td>3</td>
<td>Symptomatic cCMV</td>
<td>Oral</td>
<td>4–105 d after birth.</td>
<td>26/0</td>
<td>/</td>
</tr>
<tr>
<td>Pasternak31</td>
<td>2</td>
<td>Isolated hearing loss</td>
<td>IV and oral</td>
<td>Within the first 12 wk of life.</td>
<td>59/0</td>
<td>55.7</td>
</tr>
<tr>
<td>Royackers32</td>
<td>3</td>
<td>Symptomatic cCMV</td>
<td>IV</td>
<td>Within first month of life.</td>
<td>8/90</td>
<td>64.8 (mean)</td>
</tr>
<tr>
<td>Suganuma33</td>
<td>2</td>
<td>/</td>
<td>Oral</td>
<td>Age of 0–46 mo</td>
<td>26/0</td>
<td>/</td>
</tr>
<tr>
<td>Turriziani34</td>
<td>2</td>
<td>1) Symptomatic cCMV 2) Asymptomatic cCMV</td>
<td>Oral</td>
<td>Within first month of life.</td>
<td>36/0</td>
<td>50.7 (mean)</td>
</tr>
</tbody>
</table>

Design: 1 = case series / 2 = retrospective cohort study / 3 = prospective cohort study / 4 = randomized controlled trial.

cCMV = congenital cytomegalovirus; IV = intravenous.
TABLE II.
Overview of the Posttreatment Hearing Outcome for Children With cCMV (18 Studies).

<table>
<thead>
<tr>
<th>First Author (Reference)</th>
<th>Hearing Improvement</th>
<th>Stable Hearing</th>
<th>Hearing Deterioration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kimberlin24</td>
<td>12/31 (38.7%) total ears with SNHL at baseline</td>
<td>15/31 (48.4%) total ears with SNHL at baseline</td>
<td>4/31 (12.9%) total ears with SNHL at baseline</td>
</tr>
<tr>
<td></td>
<td>11/17 (64.7%) total ears without SNHL at baseline</td>
<td>11/17 (64.7%) total ears without SNHL at baseline</td>
<td>6/17 (35.3%) total ears without SNHL at baseline</td>
</tr>
<tr>
<td>Michaels29</td>
<td>2/7 (28.6%) total ears with SNHL at baseline</td>
<td>7/7 (100.0%) total ears with SNHL at baseline</td>
<td>0/7 (0.0%) total ears with SNHL at baseline</td>
</tr>
<tr>
<td></td>
<td>11/11 (100.0%) total ears without SNHL at baseline</td>
<td>11/11 (100.0%) total ears without SNHL at baseline</td>
<td>0/11 (0.0%) total ears without SNHL at baseline</td>
</tr>
<tr>
<td>Amir18</td>
<td>12/21 (57.1%) total ears with SNHL at baseline</td>
<td>8/21 (38.1%) total ears with SNHL at baseline</td>
<td>1/21 (4.8%) total ears with SNHL at baseline</td>
</tr>
<tr>
<td></td>
<td>25/25 (100.0%) total ears without SNHL at baseline</td>
<td>0/25 (0.0%) total ears without SNHL at baseline</td>
<td></td>
</tr>
<tr>
<td>del Rosal21</td>
<td>7/16 (43.8%) total ears with SNHL at baseline</td>
<td>9/16 (56.3%) total ears with SNHL at baseline</td>
<td>0/16 (0.0%) total ears with SNHL at baseline</td>
</tr>
<tr>
<td></td>
<td>8/8 (100.0%) total ears without SNHL at baseline</td>
<td>0/8 (0.0%) total ears without SNHL at baseline</td>
<td></td>
</tr>
<tr>
<td>Foulon23</td>
<td>3/8 (37.5%) total ears with SNHL at baseline</td>
<td>3/8 (37.5%) total ears with SNHL at baseline</td>
<td>2/8 (25.0%) total ears with SNHL at baseline</td>
</tr>
<tr>
<td></td>
<td>4/4 (100.0%) total ears without SNHL at baseline</td>
<td>4/4 (100.0%) total ears without SNHL at baseline</td>
<td>0/4 (0.0%) total ears without SNHL at baseline</td>
</tr>
<tr>
<td>Royackers22</td>
<td>2/16 (12.5%) total ears with SNHL at baseline</td>
<td>12/16 (75.0%) total ears with SNHL at baseline</td>
<td>2/16 (12.5%) total ears with SNHL at baseline</td>
</tr>
<tr>
<td>Amir17</td>
<td>29/35 (82.9%) total ears with late-onset HL</td>
<td>6/35 (17.1%) total ears with late-onset HL</td>
<td>0/35 (0.0%) total ears with late-onset HL</td>
</tr>
<tr>
<td>Bilavsky19</td>
<td>7/7 (100.0%) total ears without SNHL at baseline</td>
<td>102/102 (100.0%) total ears without SNHL at baseline</td>
<td>0/102 (0.0%) total ears without SNHL at baseline</td>
</tr>
<tr>
<td>Kimberlin26</td>
<td>8/37 (21.6%) total ears with SNHL at baseline</td>
<td>24/37 (64.9%) total ears with SNHL at baseline</td>
<td>5/37 (13.5%) total ears with SNHL at baseline</td>
</tr>
<tr>
<td></td>
<td>83/91 (91.2%) total ears without SNHL at baseline</td>
<td>83/91 (91.2%) total ears without SNHL at baseline</td>
<td>8/91 (8.8%) total ears without SNHL at baseline</td>
</tr>
<tr>
<td>Bilavsky20</td>
<td>50/77 (64.9%) total ears with SNHL at baseline</td>
<td>22/77 (28.6%) total ears with SNHL at baseline</td>
<td>5/77 (6.5%) total ears with SNHL at baseline</td>
</tr>
<tr>
<td>Mazzaferr26</td>
<td>9/14 (64.3%) total ears with SNHL at baseline</td>
<td>5/14 (35.7%) total ears with SNHL at baseline</td>
<td>0/14 (0.0%) total ears with SNHL at baseline</td>
</tr>
<tr>
<td>Koyano26</td>
<td>3/14 (21.4%) total ears with SNHL at baseline</td>
<td>1/14 (7.1%) total ears with SNHL at baseline*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6/6 (100.0%) total ears without SNHL at baseline</td>
<td>6/6 (100.0%) total ears without SNHL at baseline</td>
<td></td>
</tr>
<tr>
<td>Pasternak27</td>
<td>55/80 (68.8%) total ears with SNHL at baseline</td>
<td>23/80 (28.6%) total ears with SNHL at baseline</td>
<td>2/80 (2.5%) total ears with SNHL at baseline</td>
</tr>
<tr>
<td></td>
<td>38/38 (100.0%) total ears without SNHL at baseline</td>
<td>38/38 (100.0%) total ears without SNHL at baseline</td>
<td>0/38 (0.0%) total ears without SNHL at baseline</td>
</tr>
<tr>
<td>Lackner27</td>
<td>16/29 (55.2%) total ears with SNHL at baseline</td>
<td>11/29 (37.9%) total ears with SNHL at baseline</td>
<td>2/29 (6.9%) total ears with SNHL at baseline</td>
</tr>
<tr>
<td></td>
<td>20/23 (86.9%) total ears without SNHL at baseline</td>
<td>20/23 (86.9%) total ears without SNHL at baseline</td>
<td>3/23 (13.0%) total ears without SNHL at baseline</td>
</tr>
<tr>
<td>Ohyama30</td>
<td>68/87 (78.2%) total ears with SNHL at baseline</td>
<td>13/87 (14.9%) total ears with SNHL at baseline*</td>
<td>2/87 (2.3%) total ears with SNHL at baseline*</td>
</tr>
<tr>
<td>Sugaranuma13</td>
<td>9/38 (23.7%) total ears with SNHL at baseline</td>
<td>29/38 (76.3%) total ears with SNHL at baseline</td>
<td>0/38 (0.0%) total ears with SNHL at baseline</td>
</tr>
<tr>
<td></td>
<td>14/14 (100.0%) total ears without SNHL at baseline</td>
<td>14/14 (100.0%) total ears without SNHL at baseline</td>
<td>0/14 (0.0%) total ears without SNHL at baseline</td>
</tr>
<tr>
<td>Turriziani34</td>
<td>5/5 (100.0%) total ears with SNHL at baseline</td>
<td>62/65 (95.4%) total ears without SNHL at baseline</td>
<td>0/5 (0.0%) total ears with SNHL at baseline</td>
</tr>
<tr>
<td></td>
<td>3/65 (4.6%) total ears without SNHL at baseline</td>
<td>3/65 (4.6%) total ears without SNHL at baseline</td>
<td></td>
</tr>
</tbody>
</table>

*For some hearing-impaired ears, it was not clear whether the hearing remained stable or deteriorated.
HL = hearing loss; SNHL = sensorineural hearing loss.

Hearing Outcome for Treated Versus Untreated cCMV (Meta-analysis)
To compare hearing evolution between treated and untreated children, a meta-analysis was performed.

Figure 2A represents the forest plot of hearing improvement for cCMV-related hearing loss at birth. Treating children having hearing loss at birth with (val)ganciclovir resulted in significantly more hearing improvement (Peto
OR 7.72, 95% CI 3.08–19.34; P < .001; I² 9%, low heterogeneity). Assuming an improvement rate of 8.3% in the untreated group reported by Goderis et al.,36 we found an improvement rate of 41.1% in the treated group. Also hearing deterioration was significantly reduced by antiviral treatment for children with hearing impairment at birth (Peto OR 0.23, 95% CI 0.10–0.57; P = .001; I² 83%, considerable heterogeneity) (Figure 2B). This resulted in a deterioration rate of 7.4% in the treated group relative to an assumed deterioration rate of 25.7% in the untreated group.

Fig. 2. Forest plots of (A) hearing improvement for cCMV-related hearing loss at birth, (B) hearing deterioration for cCMV-related hearing loss at birth, and (C) hearing deterioration for ears without hearing loss at birth. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

Fig. 3. Forest plots of (A) hearing improvement for children with symptomatic cCMV and hearing loss at birth and (B) hearing deterioration for children with symptomatic cCMV and hearing loss at birth. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]
The results for children without hearing loss at birth are represented in Figure 2C. Treating children without hearing loss at birth did not result in significantly less hearing deterioration (Peto OR 0.34, 95% CI 0.11–1.09; \( P = .07; \theta^2 \), low heterogeneity).

Abovementioned results apply to the group of children with symptomatic cCMV, asymptomatic cCMV, isolated hearing loss, and late-onset hearing loss. A second aim of this study was to differentiate between subgroups of cCMV. (Val)ganciclovir resulted in significantly more hearing improvement for children with symptomatic cCMV and hearing loss at birth (Peto OR 7.72, 95% CI 2.33–25.63; \( P < .001; \theta^2 \), low heterogeneity) (Figure 3A). Relative to an assumed improvement rate of 9.4% in the untreated group, treated children experienced an improvement rate of 44.5%. Treating children with symptomatic cCMV with hearing loss at birth also resulted in significantly less hearing deterioration (Peto OR 0.17, 95% CI 0.07–0.45; \( P < .001; \theta^2 \), substantial heterogeneity) (Figure 3B). Goderis et al.\(^{36}\) reported a deterioration rate of 28.2% in the untreated group; relative to these previous findings, we found a deterioration rate of 6.3% in the treated group. Given the limited number of studies, we could not draw conclusions for symptomatic children without hearing loss, asymptomatic children, children with isolated hearing loss, or late-onset hearing loss.

**Effect of Treatment Related to Degree of Baseline Hearing Loss**

Hearing improvement after therapy was related to the severity of baseline hearing loss in 7/18 included studies in this systematic review.\(^{17,20–22,30,31,33}\) These findings are reported in Figure 4. In general, all studies reported more posttreatment hearing improvement in patients with mild to moderate hearing loss compared to severe hearing loss. The results of Amir et al.\(^{17}\) are not represented in this table. They reported more improvement after therapy for mild or moderate hearing loss compared to severe hearing loss but did not mention absolute numbers.\(^{17}\)

**Effect of Treatment Related to Treatment Protocol**

A comparison between treatment protocols has been made by six of the 18 included studies. Comparing 6 weeks of oral ganciclovir with 6 months, Kimberlin et al.\(^{25}\) found no difference between both groups at 6 months, which is similar to the findings of Ohyama.

---

TABLE III. Findings of This Study and Recommendations for Future Research.

Findings

1. Treating symptomatic children with hearing loss at birth resulted in more hearing improvement and less hearing deterioration compared to untreated symptomatic children.
2. Relative to an improvement and deterioration rate of 9.4% and 28.2% in an untreated group of symptomatic children with hearing loss, the improvement and deterioration rate of the treated group was 44.5% and 6.3%, respectively.
3. There is insufficient evidence of the potential beneficial role of (val)ganciclovir on hearing outcome of children with:
   - isolated hearing loss
   - late-onset hearing loss
   - asymptomatic cCMV

Recommendations for future research

1. Hearing loss categories need to be standardized.
2. Stable, improved, and deteriorated hearing loss need to be defined and standardized.
3. The definition for symptomatic cCMV, asymptomatic cCMV, isolated hearing loss, and late-onset hearing loss should be standardized.
4. There is an urgent need for future prospective, randomized, blinded clinical trials with well-defined outcome measurements. Focus should be laid on the potential beneficial effect of (val)ganciclovir on cCMV-related hearing outcome for children with isolated hearing loss and late-onset hearing loss.
et al., but they described significantly more stable or improved hearing in the 6 months group after 12 and 24 months. Pasternak et al. reported the same hearing outcomes for a combination with ganciclovir and valganciclovir compared to monotherapy with valganciclovir. Another comparison has been made for perinatally (treatment before the age of 1 month) and postnatally treated patients (initiation of therapy after the age of 1 month). Two studies reported hearing outcome for both groups. Analyzing ears with hearing impairment at baseline, Bilavsky et al. found hearing improvement in 15/22 (68.2%) ears treated postnatally and 50/77 (64.9%) ears treated perinatally. Pasternak et al. investigated children with bilateral hearing loss at birth. Relative to an improvement and deterioration rate of treated children with hearing loss at birth varied between 41.1% and 44.5% and 6.3% and 7.4%, respectively. Furthermore, treatment may be most favorable for children with mild to moderate hearing loss. We did not find a significant effect of treating children without hearing loss at birth; however, these results were approaching statistical significance. Still today, there is insufficient evidence of the potential beneficial role of (val)ganciclovir on hearing outcome of children with isolated hearing loss, late-onset hearing loss, and asymptomatic cCMV (Table III). Future research should focus on the potential beneficial effect of (val)ganciclovir on cCMV-related hearing outcome especially for children with isolated hearing loss and late-onset hearing loss.

The included studies investigated the effect of (val)ganciclovir on cCMV-related hearing loss during the period 1991 to 2018. In the nineties, treatment consisted of intravenous ganciclovir. As the oral bioavailability of ganciclovir is too low, it should be administered intravenously, which entail a higher risk of infections. Given the complications and logistical challenges associated with long-term intravenous access, the need for oral administration resulted in the use of valganciclovir. Over the years, not only a change in route of administration has occurred but treatment has also been prolonged. A pioneering study of Kimberlin et al. proved that therapy for 6 months has a higher beneficial effect on hearing and developmental outcomes compared to 6 weeks. Based on this study, a lot of researchers changed their treatment protocol during the course of the study. These changes in treatment protocols over the years resulted in a high intra- and interstudy variability of dose, duration, and route of administration.

Moreover, treatment is associated with the fear for side effects: neutropenia, transiently raised aminotransferases, and thrombocytopenia. These are dose-dependent and reversible after dose reduction. In contrast with short-term, long-term side effects are poorly known and may cause concern. Animal models showed impaired fertility and carcinogenic toxicity but similar findings have not been found in humans. The fertility and carcinogenic toxicity but similar findings have not been found in humans. Today, it is generally only recommended to treat children with moderately to severely symptomatic cCMV because their symptom severity exceeds the risk for side effects. Therefore, the number of studies treating isolated hearing loss, late-onset hearing loss, or asymptomatic cCMV and their sample size is rather limited (Table I).

Another concern of treatment is the selection of resistant viral variants. Resistance has been reported for both ganciclovir and valganciclovir; this is suggested by an increase in viral load some weeks to months after therapy initiation. A particular dose or treatment duration has not yet been linked to onset of resistance. In order to monitor resistance onset, weight-based dosing and a monthly surveillance of viral load should be performed.

Furthermore, concerns about only a short-term treatment effect have already been expressed. A long-term follow-up is recommended to evaluate the effect of antiviral therapy on the long-term. Postnatal treatment of patients and the latest age at which intervention is possibly advantageous is another point of ongoing interest.

**Adverse Effects**

Of the 18 included studies, 16 investigated the side effects of antiviral treatment. The most frequently mentioned adverse effect of antiviral treatment is neutropenia. The definition of neutropenia, however, differed between authors. Supporting Table 5 represents the side effects for the 11 treatment protocols more in detail. Kimberlin et al. compared development of neutropenia between ganciclovir (6 mg/kg/dose every 12 hours for 6 weeks) and a control group, respectively, 63% (29/46) and 21% (9/43) of the children developed neutropenia (P < .01). Oral valganciclovir (16 mg/kg/dose in 2 daily doses) for 6 weeks or 6 months was found to result in the same percentage of neutropenia. Furthermore, the risk of neutropenia is the highest in the first 3 months of treatment. The extent varies from mild to severe; dose adjustment was sometimes required. Other less frequent side effects were catheter infections (intravenous ganciclovir), transiently raised aminotransferases, and thrombocytopenia (platelets <100,000 mm³). From the 18 included studies, none reported resistance even though some patients were treated for 1 year.

**DISCUSSION**

‘Who, when and how to treat?’ is still the main question for treating cCMV-related hearing loss. This systematic review was performed to search for existing evidence of a beneficial effect of (val)ganciclovir on hearing in children with cCMV infection and to identify future research questions. A meta-analysis was performed to compare hearing evolution between treated and untreated ears. Our meta-analysis showed that (val)ganciclovir resulted in significantly more hearing improvement and less hearing deterioration for children with cCMV-related hearing loss at birth. A subgroup analysis showed comparable results for symptomatic children with hearing loss at birth. Relative to an improvement and deterioration rate of 9.4% and 28.2% in an untreated group, the improvement and deterioration rate of treated children with hearing loss at birth varied between 41.1% and 44.5% and 6.3% and 7.4%, respectively. Furthermore, treatment may be most favorable for children with mild to moderate hearing loss. We did not find a significant effect of treating children without hearing loss at birth; however, these results were approaching statistical significance. Still today, there is insufficient evidence of the potential beneficial role of (val)ganciclovir on hearing outcome of children with isolated hearing loss, late-onset hearing loss, and asymptomatic cCMV (Table III). Future research should focus on the potential beneficial effect of (val)ganciclovir on cCMV-related hearing outcome especially for children with isolated hearing loss and late-onset hearing loss.

The included studies investigated the effect of (val)ganciclovir on cCMV-related hearing loss during the period 1991 to 2018. In the nineties, treatment consisted of intravenous ganciclovir. As the oral bioavailability of ganciclovir is too low, it should be administered intravenously, which entail a higher risk of infections. Given the complications and logistical challenges associated with long-term intravenous access, the need for oral administration resulted in the use of valganciclovir. Over the years, not only a change in route of administration has occurred but treatment has also been prolonged. A pioneering study of Kimberlin et al. proved that therapy for 6 months has a higher beneficial effect on hearing and developmental outcomes compared to 6 weeks. Based on this study, a lot of researchers changed their treatment protocol during the course of the study. These changes in treatment protocols over the years resulted in a high intra- and interstudy variability of dose, duration, and route of administration.

Moreover, treatment is associated with the fear for side effects: neutropenia, transiently raised aminotransferases, and thrombocytopenia. These are dose-dependent and reversible after dose reduction. In contrast with short-term, long-term side effects are poorly known and may cause concern. Animal models showed impaired fertility and carcinogenic toxicity but similar findings have not been found in humans. Today, it is generally only recommended to treat children with moderately to severely symptomatic cCMV because their symptom severity exceeds the risk for side effects. Therefore, the number of studies treating isolated hearing loss, late-onset hearing loss, or asymptomatic cCMV and their sample size is rather limited (Table I).

Another concern of treatment is the selection of resistant viral variants. Resistance has been reported for both ganciclovir and valganciclovir; this is suggested by an increase in viral load some weeks to months after therapy initiation. A particular dose or treatment duration has not yet been linked to onset of resistance. In order to monitor resistance onset, weight-based dosing and a monthly surveillance of viral load should be performed.

Furthermore, concerns about only a short-term treatment effect have already been expressed. A long-term follow-up is recommended to evaluate the effect of antiviral therapy on the long-term. Postnatal treatment of patients and the latest age at which intervention is possibly advantageous is another point of ongoing interest.
The main limitation of this systematic review is the low-quality design of the included studies and the high heterogeneity. Most studies consisted of a retrospective design and lack a control group. Of the included studies, only two were randomized prospective clinical trials, both investigating posttreatment hearing outcome of symptomatic cCMV. As hearing fluctuations may occur in cCMV-related hearing loss, it might be possible that children spontaneously experience hearing improvement even without treatment. A control group may overcome this limitation in the future. In addition, duration of follow-up was rather short (median time of follow-up: 45.5 months). Heterogeneity between studies was high and reflected in many ways. First, the change in defining symptomatic cCMV over the years complicates a comparison of the different studies. Second, this systematic review represents hearing outcome at last follow-up but timing of last follow-up differed between studies as well as onset of therapy. Third, multiple definitions of hearing improvement and hearing outcome (total ear analysis, best ear analysis, number of children, etc.) were used. Moreover, the change of hearing threshold of some included studies might not be clinically relevant. In conclusion, abovementioned heterogeneity complicates comparison between studies and may have led to the loss of subtle differences between studies. We underline the need to develop international standardized definitions and treatment protocols. The urgent need for future prospective, randomized clinical trials still exists (Table III).

CONCLUSION

Treating symptomatic children with hearing loss results in more hearing improvement and less deterioration compared to untreated children. Furthermore, treatment may be most favorable for children with mild to moderate hearing loss. Still today, there is insufficient evidence of the potential beneficial role of (val)ganciclovir on hearing outcome of children with isolated hearing loss, late-onset hearing loss, and asymptomatic cCMV. Future research should focus on the potential beneficial effect of (val)ganciclovir on cCMV-related hearing outcome especially for children with isolated hearing loss and late-onset hearing loss. A standardization of definitions and treatment protocols would create uniformity in future studies.

AUTHOR CONTRIBUTIONS

Prof. Dr. Ingeborg Dhooge and Dr. Annelies Keymeulen conceptualized and designed the study and critically reviewed and revised the article for important intellectual content. Dr. Frederic Acke conceptualized and designed the study as well, performed study inclusion, data extraction, and quality assessment. Finally, he critically reviewed and revised the article for important intellectual content. Dr. Elise De Cuyper performed study inclusion, data extraction, quality assessment, interpretation of data, and wrote the article. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

ABBREVIATIONS

cCMV congenital cytomegalovirus infection
CNS central nervous system
SNHL sensorineural hearing loss

BIBLIOGRAPHY


