Long-Term Hearing Outcomes of Symptomatic Congenital CMV Infected Children Treated with Valganciclovir

Hilary McCrary MD MPH, Xiaoming Sheng PhD, Tom Greene PhD, Albert Park MD

University of Utah
Disclosures:

• NIH U01 PI CMV multi-institutional study (Park)
• NIDCD R01 co-I Cochlear Implantation (Park)
• Valganciclovir – not FDA approved for congenital CMV
Symptomatic Congenital CMV Infection (sCMV)

- Approximately 10%
- Fetal demise
- Prematurity
- Common features:
  - Hepatomegaly
  - Splenomegaly
  - Petechiae
  - IUGR
  - Jaundice
  - Microcephaly
  - Chorioretinitis
  - Sensorineural hearing loss (50%)
Hearing Loss Disease Burden sCMV (annual):

- cCMV-infected newborns (19,600)
  - Symptomatic (2000/yr)
    - Hearing loss (1000/yr)
    - Normal Hearing (1000/yr)
  - Asymptomatic (14,000/yr)
  - CHIP (3600/yr)

Characteristics of sCMV Induced Hearing Loss:

Treating the Symptomatic cCMV Infected Infant:

• Symptomatic CMV is treatable!
• General consensus that this group would benefit from antiviral therapy (valganciclovir or VGCV)
Valganciclovir (VGCV):

- L-valyl ester prodrug of ganciclovir
- Blocks viral replication
- After oral administration, it is rapidly converted to ganciclovir by intestinal and hepatic esterases
- FDA approved to prevent CMV disease for pediatric patients receiving heart or kidney transplants
- Not FDA approved for treatment of cCMV
Six Months versus 6 weeks Valganciclovir (VGC) for infants with Symptomatic CMV

- Confirmation CMV from urine or throat swab-culture, shell vial or PCR
- Symptomatic CMV (1 or more): thrombocytopenia, petechiae, HSM, IUGR, hepatitis, CNS involvement (hearing loss, radiographic, CMV in CSF)
- <30 days

Kimberlin D et al. NEJM 2015
Six Months versus 6 weeks Valganciclovir (VGC) for infants with Symptomatic CMV
Results:

• Primary outcome- best ear hearing at 6 months – NS

• Secondary- Total ear hearing (hearing in one or both ears that could be evaluated) was more likely to be improved or to remain normal at 12 months in the 6-month group (73% vs. 57%, P = 0.01).
6 Weeks vs. 6 Months Valganciclovir Hearing Outcomes @ Two year Followup

6 Weeks of Treatment

- 36% Improved or Remained Normal
- 64% Worse or remained abnormal

6 Months of Treatment

- 23% Improved or Remained Normal
- 77% Worse or remained abnormal

P = 0.04

Kimberlin et al. NEJM 2015
### 6 Weeks vs. 6 Months Valganciclovir Bayley III Outcomes 24 mo.

<table>
<thead>
<tr>
<th>Measure</th>
<th>6 Week Therapy</th>
<th>6 Month Therapy</th>
<th>Adjusted P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive Composite</td>
<td>76.0±2.6</td>
<td>84.4±2.6</td>
<td>0.0236</td>
</tr>
<tr>
<td>Language Composite</td>
<td>72.5±2.9</td>
<td>84.6±2.9</td>
<td><strong>0.0037</strong></td>
</tr>
<tr>
<td>Receptive Communication Scale</td>
<td>5.2±0.5</td>
<td>7.3±0.5</td>
<td><strong>0.0027</strong></td>
</tr>
<tr>
<td>Expressive Communication Scale</td>
<td>5.5±0.5</td>
<td>7.3±0.5</td>
<td>0.0158</td>
</tr>
<tr>
<td>Motor Composite</td>
<td>74.1±3.2</td>
<td>85.5±3.3</td>
<td>0.0130</td>
</tr>
<tr>
<td>Fine Motor Scale</td>
<td>6.4±0.6</td>
<td>8.0±0.6</td>
<td>0.0566</td>
</tr>
<tr>
<td>Gross Motor Scale</td>
<td>5.3±0.5</td>
<td>7.0±0.5</td>
<td>0.0198</td>
</tr>
</tbody>
</table>

P-values < 0.0071 (=0.05/7) considered statistically significant using Bonferroni adjustment for multiple testing
Safety Measures:

- Grade 3 or 4 neutropenia 19% of the participants during the first 6 weeks.
- During the next 4.5 months of the study, grade 3 or 4 neutropenia -21% (6 month) vs 27% of (6-week: P = 0.64)
- 3 temporary suspension drug b/c ANC< 500
- All resumed and occurred first 6 weeks
Role of VGCV in sCMV patients:

“Based upon this study, it can be concluded that a 6-month course of oral VGCV is a well-tolerated and effective therapeutic option for infants with symptomatic congenital CMV infection.”

Clinical Question:

What is the **long-term** hearing outcomes among symptomatic patients with congenital CMV infection (cCMV) treated with VGCV?
Methods:

• A retrospective chart review of symptomatic cCMV patients treated with VGCV (2003-2017)
• cCMV diagnosis: saliva or urine PCR testing first 3 weeks of life or positive CMV PCR DBS > 3 weeks of age
• Symptomatic cCMV defined as having one or more conditions

Thrombocytopenia, IUGR, microcephaly, intracranial calcifications, hepatitis, petechiae, hepatosplenomegaly
Methods:

• Baseline ABR testing
• ABR or behavioral testing afterwards
• Regular audiologic assessments- average 5.8 per patient
Methods:

• The primary endpoint was the change between baseline and follow-up in the hearing scores corresponding to the best ear at each audiologic follow-up (Kimberlin et al NEJM 2015)

• Measure of “functional” hearing
Methods:

Secondary Measures:

1. Mean change in thresholds by ear
2. Clinically significant worsening hearing in either ear was defined as the occurrence of either:
   - a) 10 dB or greater increase in minimum response level at both 2 and 4 kHz
   - b) 15 dB or greater increase at either frequency
   - c) Cochlear implantation
3. Proportion of best vs worse ear that deteriorates first
4. Time hearing deterioration
Results:

- N=16 symptomatic cCMV infected children treated with VGCV
- 10 female; 6 male
- One-third had 2 or more sxs assoc w cCMV
- None had normal hearing at baseline
- Average VGCV duration: 93± 67 days
- Mean FU: 3.2 years (range 0.3-10.0 years)

![Table 1: Characteristics of Study Participants](image)
Results:

- Measurable worsening but NS in baseline and FU best-ear
- Mean worsening change 11.9 dB (95% CI: -1.1 to 24.9 dB, positive value denotes worsening p=0.07
Results:

- 14/16 patients (87.5%, p-value<0.001) were found to have clinically significant worsening in hearing
- Total change scores right ear 15.5 dB (95% CI: 1.5-29.3, p=0.03)
- Total change scores left ear 14.2 dB (95% CI: 2.2-26.2, p=0.02)
- Mean elapsed time for progression: 2.6± 0.2 years (range 0.3-4.1 years)
- 10 patients candidates for CI, 2 currently have CI
Results:

• Comparison Best vs Worse Ear over time
  a. No change n=2
  b. Change same time n=3
  c. Best ear deteriorates first n=3
  d. Worse ear deteriorates first n=3

• No difference outcomes based on duration of antiviral therapy or age when therapy started
Summary:

• First study report progressive HL in sCMV treated with VGCV beyond 2 years
• Primary outcome of change in best ear hearing score from baseline was not statistically significant
• Statistically significant worsening of each ear over time
• 14 of 16 participants had worsening of their hearing
• No pattern for worse or better ear
• Average time to hearing deterioration 2.6 years with late progression noted more than 4 years.
Discussion:

• Natural history unrx’ed sCMV children - progressive SNHL
• Dahle et al- 40.7% sCMV dev progressive SNHL
• Studies VGCV for sCMV – relatively short FU
• Kimberlin et al (2015)
• Amir et al (2010)- 1 yr FU rx’ed sCMV – no control
• Koyano et al (2018) 10 sCMV rxed to 7 unrxed
Unclear hearing outcomes
Limitations:

- Small sample size
- Half cohort – antiviral rx older than 1 month of age
- All treated when under 1 mo of age developed progressive SNHL
- Variability rx duration- no data for 6 mo until 2015 NEJM study. NO difference outcome based on VGCV duration
- Variation FU- may be underestimating hearing loss progression
- No control group better characterize VGCV effect
Conclusions:

• These preliminary findings suggest the need for continued close hearing surveillance of these children
• Follow-up needs to be for at least 4 years
• Both ears need to be assessed since deterioration may occur with either ear