Neonatal HSV and Congenital CMV Infections: The Intersection of Drugs, Diagnostics and the Natural History of Disease

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South Carolina Chapter of the AAP
Asheville, North Carolina
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Disclosure

- I am on the Board of Gilead Sciences and will not discuss any of their products.
- I have received remuneration from the NIH, and IDSA (Associate Editor JID).
- I serve on Data Safety and Monitoring Boards for clinical trials sponsored by the NIH, GSK, and Merck.
- My grant support is from NIAID.
- I do intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.
Objectives

- Understand the differences in the pathogenesis of congenital CMV and neonatal HSV infections
- Define diagnostic approaches
- Know therapeutic approaches to these diseases
- Be able to define outcome with therapy
Neonatal HSV and Congenital CMV Infections: The Intersection of Drugs, Diagnostics and the Natural History of Disease

1970
- Vidarabine Rx of Neonatal HSV

1980
- Vidarabine Rx of Chickenpox
- ACV Rx of Chickenpox

1990
- ACV Rx of Neonatal HSV
- PCR for HSV CNS Disease

2000
- Asympt HSV CNS Infection
- High dose ACV Rx of Neo HSV
- Oral ACV Rx of Neo HSV: PK and PD

2010
- End of Rx PCR for Persistent CNS HSV Disease
- Suppressive Rx of Neo HSV
- Valganciclovir Rx of CMV
- 6 Months of Valganciclovir Rx

New Drug Applications: Ten (Defining the Standard of Care)
Where Were We in 1980?

- Neonatal Herpes Simplex Virus (HSV) Infection
  - No Established Therapy
  - Mortality of 75%; Morbidity of 90%

- Congenital Cytomegalovirus (CMV) Infection
  - No Established Therapy
  - Mortality of 15%; Morbidity of 25%
## Therapeutic Opportunities: HSV Versus CMV Infections of the Newborn

<table>
<thead>
<tr>
<th>Herpes Simplex Virus</th>
<th>Cytomegalovirus</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Acquired during delivery</td>
<td>• Acquired early in gestation</td>
</tr>
<tr>
<td>• Usually occurs with maternal primary infection</td>
<td>• Majority of cases occur with maternal primary infection</td>
</tr>
<tr>
<td>• Relatively short incubation period</td>
<td>• Infection progresses over months</td>
</tr>
<tr>
<td>• Disease of the newborn is usually obvious</td>
<td>• Disease can be asymptomatic</td>
</tr>
<tr>
<td>• Should be amenable to therapy</td>
<td>• Should be less amenable to therapy than HSV</td>
</tr>
</tbody>
</table>
Neonatal HSV Infection: Vesicular Rash
Neonatal HSV Disease
CNS Disease
Liver with coagulative necrosis and HSV intranuclear inclusions
Pathogenesis of Neonatal HSV Infection

Maternal Genital Herpes Simplex Virus Infection

Intrauterine Infection (5%)
(transplacental or ascending)

Intrapartum Infection (85%)
Superficial Replication on Skin or Eye or in Mouth

Postnatal Infection (10%)

VIREMIA = Disseminated Disease

45% SEM

30% CNS

25% Disseminated

NEURONAL SPREAD = Localized Encephalitis
Risk of Vertical Transmission

- Factors increasing risk of transmission:
  - primary genital herpes infection, particularly in last trimester
  - no maternal HSV antibodies before pregnancy and seropositive partner
  - use of fetal scalp monitors or instrumented delivery

<table>
<thead>
<tr>
<th>Risks of Neonatal Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary genital herpes</td>
</tr>
<tr>
<td>Recurrent genital herpes</td>
</tr>
</tbody>
</table>
Intrapartum and Postpartum HSV Infection

- **Disseminated disease** ~ 25%
  - DIC
  - Pneumonia
  - Hepatitis
  - CNS involvement (60% to 75%)

- **Encephalitis (CNS disease)** ~ 30%
  - Seizures
  - Lethargy
  - Irritability
  - Poor feeding
  - Temperature instability

- **Skin, eyes, and/or mouth (SEM disease)** ~ 45%
## Characteristics of Babies with Neonatal HSV Infection

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Disease Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Disseminated</td>
</tr>
<tr>
<td>No. of babies</td>
<td>93 (32)</td>
</tr>
<tr>
<td>No. premature (&lt;36wk)</td>
<td>33 (35)</td>
</tr>
<tr>
<td>Enrollment age, days</td>
<td>11.6±0.7</td>
</tr>
<tr>
<td>Clinical findings</td>
<td></td>
</tr>
<tr>
<td>Skin lesions</td>
<td>72 (77)</td>
</tr>
<tr>
<td>Brain involvement</td>
<td>69 (74)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>46 (49)</td>
</tr>
</tbody>
</table>
Evolution of Therapy for Neonatal HSV Infections: The Early Days

• 1981 – Vidarabine (adenine arabinoside) vs. placebo
  – Mortality of DIS is decreased
  – Morbidity is improved
  – Progression from SEM to CNS or DIS decreased

• 1983 – Confirmation of controlled trial data
Survival Following Vidarabine Therapy for Babies with CNS and Disseminated Disease
Failure of Vidarabine Therapy to Improve Survival with High Dose Therapy
Evolution of Therapy for Neonatal HSV Infections: The Decades

- 1991 – Direct comparison of acyclovir and vidarabine
  No difference in mortality
- 1996 – Establishment of PCR as the gold standard of diagnosis of CNS infections: both babies and adults
- 2001 – High dose acyclovir is established as the standard of care
- 2005 – Value of end of treatment CSF PCR assessment
Diagnosis

- **Culture**
  - Skin Lesions
  - Oropharynx
  - Eye
  - Cerebrospinal Fluid
  - Stool

- **Polymerase Chain Reaction**
  - Cerebrospinal Fluid
### Sensitivity and Specificity of PCR

<table>
<thead>
<tr>
<th>PCR Status</th>
<th>Biopsy Status</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>3</td>
</tr>
<tr>
<td>Negative</td>
<td>Positive</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>44</td>
</tr>
</tbody>
</table>

- **Sensitivity**: 98%
- **Specificity**: 94%
- **Positive Predictive Value**: 95%
- **Negative Predictive Value**: 98%
Direct Comparison of Vidarabine and Acyclovir: Impact on Survival by Disease Classification

No Differences
Why Did Acyclovir Not Improve Outcome?

- Did we use the correct dose?
- Did we treat long enough?

Conclusion: Probably not – thus, we increased both dose and duration of therapy.

- But what do we not know about this disease?
Improved Mortality with High Dose Acyclovir: CNS Disease

Proportion Surviving

Months

Pediatrics 2001;108:230-238
Improved Mortality with High Dose Acyclovir Therapy: Disseminated Disease

Pediatrics 2001;108:230-238
## Definitions of Morbidity

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild</strong></td>
<td>Recurrent keratoconjunctivitis</td>
</tr>
<tr>
<td></td>
<td>Mild motor delay (no hemiparesis)</td>
</tr>
<tr>
<td></td>
<td>Minimal Speech delay</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>With/Without Hemiparesis</td>
</tr>
<tr>
<td></td>
<td>Persistent seizure disorder</td>
</tr>
<tr>
<td></td>
<td>&lt; 3 month developmental delay</td>
</tr>
<tr>
<td><strong>Severe</strong></td>
<td>Microcephaly</td>
</tr>
<tr>
<td></td>
<td>Spastic quadriplegia</td>
</tr>
<tr>
<td></td>
<td>Blindness/chorioretinitis</td>
</tr>
<tr>
<td></td>
<td>&gt; 3 month developmental delay</td>
</tr>
</tbody>
</table>
Morbidity Among Survivors With Known Outcomes (High versus Low Dose) After 12 Months

Percentage mg/kg/day

SEM Disease

CNS Disease

Disseminated Disease

0 20 40 60 80 100

Severe
Moderate
Mild
Normal

Pediatrics 2001;108:230-238
# Prognostic Factors

## SEM Disease

<table>
<thead>
<tr>
<th>Dominant Factors</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mortality</td>
</tr>
<tr>
<td># of cutaneous recurrences</td>
<td></td>
</tr>
<tr>
<td>&lt; 3</td>
<td>NA</td>
</tr>
<tr>
<td>≥ 3</td>
<td>NA</td>
</tr>
<tr>
<td>Virus Type</td>
<td></td>
</tr>
<tr>
<td>HSV-1</td>
<td>NA</td>
</tr>
<tr>
<td>HSV-2</td>
<td>NA</td>
</tr>
</tbody>
</table>

Confounding Variables

- Is SEM disease really SEM disease?

- What have we learned about PCR evaluation of the CSF at the conclusion of therapy?

- Risk factors for impaired neurologic outcome with SEM disease imply chronic replication in the CNS – can we prove it?
Why Do Babies With Disease Apparently Localized to Skin, Eye, Mouth Develop Neurologic Impairment?

8/11  PCR positive for HSV DNA in CSF at presentation with normal CSF findings

11/11  >3 recurrences first 3 months post-therapy

Proof of asymptomatic infection of the CNS
End of Therapy PCR Evaluation: Impact of Disease Classification

<table>
<thead>
<tr>
<th>Infant Characteristic</th>
<th>PCR Negative* (N=11)</th>
<th>PCR Positive** (N=19)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diseases Classification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS</td>
<td>4 (36.4%)</td>
<td>14 (73.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Disseminated</td>
<td>0 (0.0%)</td>
<td>5 (26.3%)</td>
<td></td>
</tr>
<tr>
<td>SEM</td>
<td>7 (63.6%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Antiviral Therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vidarabine</td>
<td>2 (18.2%)</td>
<td>13 (68.4%)</td>
<td>=0.008</td>
</tr>
<tr>
<td>Acyclovir</td>
<td>9 (81.8%)</td>
<td>6 (31.6%)</td>
<td></td>
</tr>
</tbody>
</table>

* Only negative PCR results from CSF specimens obtained after treatment
** At least one positive PCR result from CSF specimens obtained after therapy
## End of Therapy PCR Evaluation: By Virus Type

<table>
<thead>
<tr>
<th>Infant Characteristic</th>
<th>PCR Negative* (N=11)</th>
<th>PCR Positive** (N=19)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Viral Type</strong></td>
<td></td>
<td></td>
<td>P&lt;0.018</td>
</tr>
<tr>
<td>HSV-1</td>
<td>5 (45.4%)</td>
<td>2 (10.5%)</td>
<td></td>
</tr>
<tr>
<td>HSV-2</td>
<td>5 (45.4%)</td>
<td>17 (89.5%)</td>
<td></td>
</tr>
<tr>
<td>Not typed</td>
<td>1 (9.1%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
</tbody>
</table>

* Only negative PCR results from CSF specimens obtained after treatment

** At least one positive PCR result from CSF specimens obtained after therapy
Morbidity And Mortality By Virus Type

- HSV-1
- HSV-2

Percentage
- Dead
- Severe
- Moderate
- Mild
- Normal

SEM Disease
- HSV-1
- HSV-2

CNS Disease
- HSV-1
- HSV-2

Disseminated Disease
- HSV-1
- HSV-2

Graph legend:
- Red: Dead
- Orange: Severe
- Light blue: Moderate
- Pink: Mild
- Green: Normal
End of Therapy PCR Evaluation: Neurologic Outcome

<table>
<thead>
<tr>
<th>Infant Characteristic</th>
<th>PCR Negative* (N=11)</th>
<th>PCR Positive** (N=19)</th>
<th>P&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morbidity and mortality after 12 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>6 (54.5%)</td>
<td>1 (5.3%)</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>1 (9.1%)</td>
<td>3 (15.8%)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>2 (18.2%)</td>
<td>10 (52.6%)</td>
<td></td>
</tr>
<tr>
<td>Dead</td>
<td>0 (0.0%)</td>
<td>5 (26.3%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (18.2%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
</tbody>
</table>

* Only negative PCR results from CSF specimens obtained after treatment
** At least one positive PCR result from CSF specimens obtained after therapy
Defining the Requirement for End of Treatment PCR Assessment of the CSF: 
Neurologic Outcome and PCR Status*

*Completion of therapy
Does Suppressive Acyclovir Therapy Improve Outcome of Neonatal Herpes?

- To determine if suppressive oral acyclovir therapy improves neurologic outcome
- To determine if continuous administration of oral acyclovir suspension suppresses recurrent skin lesions following neonatal HSV disease

Neonatal HSV Suppression Studies

Endpoints

• Primary endpoint
  – Neurologic impairment at 12 months of life
  – Bayley Scales of Infant Development

N Engl J Med
2011;365(14):1284-92
# Bayley Mental Score at 12 Months

<table>
<thead>
<tr>
<th></th>
<th>CNS Disease</th>
<th>SEM Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acyclovir</td>
<td>Placebo</td>
</tr>
<tr>
<td>N=16</td>
<td>90.5</td>
<td>66.5</td>
</tr>
<tr>
<td>N=12</td>
<td>88.24†</td>
<td>68.12†</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted Mean</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value by ANCOVA</td>
<td>0.046*</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for covariates at baseline which were unbalanced between treatment groups:
†Head circumference at birth, birth weight, enrollment weight
‡Enrollment weight

*Adjusted for covariates at baseline which were unbalanced between treatment groups:
†Head circumference at birth, birth weight, enrollment weight
‡Enrollment weight
Neonatal HSV Encephalitis
Bayley Mental Score at 1 Year

Acyclovir (N=16)
Median = 90.5  Mean= 88.24

Placebo (N=12)
Median = 66.5  Mean= 68.12

\[ P-value = 0.046 \]
Bayley Mental Score at 12 Months

CNS Disease

60 mg/kg/d + placebo

60 mg/kg/d + suppression

Severe
Moderate
Mild
Normal

n=11
n=13

Percentage

P=0.04
Bayley Mental Score at 12 Months

CNS Disease

30 mg/kg/d

60 mg/kg/d

P > 0.13

n=28

n=13

Severe

Moderate

Mild

Normal

60 mg/kg/d + placebo

60 mg/kg/d + suppression

P = 0.04

n=11

n=13

Percentage

mg/kg/d
Prevention of Cutaneous Recurrences
Time to Blinded Drug Discontinuation

Log rank
P = 0.0085
Conclusions

• Improved neurologic outcomes occur when babies are started immediately on suppressive oral acyclovir therapy for six months – should we treat longer?

• Following both CNS and SEM disease, antiviral suppression diminishes skin lesion recurrences

• While neutropenia is not statistically associated with suppressive therapy, the P-value approaches statistical significance

Road to the Future

- Combination therapy with brincidofovir (CMX 001) or pretilovir for acute disease
- Suppressive therapy with valacyclovir for a longer time
- Can this disease be prevented?
  - Maternal vaccination
  - At delivery PCR and prophylaxis of the newborn
Congenital Cytomegalovirus Infection
CMV Infection in Pregnancy

Primary Maternal CMV Infection

40% Transmission to Fetus

10-15% infected infants may have clinically apparent disease (mild to severe)

- 10% develop normally
- 90% develop sequelae

85-90% infected infants are asymptomatic

- 5-15% develop sequelae
- 85-95% develop normally

## Sequelae Following Fetal Disease/Infection

<table>
<thead>
<tr>
<th>Sequelae</th>
<th>Symptomatic</th>
<th>Asymptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensorineural hearing loss</td>
<td>58% (58/100)</td>
<td>7.4% (22/299)</td>
</tr>
<tr>
<td>Bilateral hearing loss</td>
<td>37% (37/100)</td>
<td>2.7% (8/299)</td>
</tr>
<tr>
<td>Speech threshold moderate to profound (60 to 90 dB)</td>
<td>27% (27/100)</td>
<td>1.7% (5/299)</td>
</tr>
<tr>
<td>Chorioretinitis</td>
<td>20.4% (19/93)</td>
<td>2.5% (7/281)</td>
</tr>
<tr>
<td>IQ &lt; 70</td>
<td>55% (33/60)</td>
<td>3.7% (6/159)</td>
</tr>
<tr>
<td>Microcephaly, seizures, or paresis/paralysis</td>
<td>51.9% (54/104)</td>
<td>2.7% (9/330)</td>
</tr>
</tbody>
</table>

*Infectious Diseases of the Fetus and Newborn Infant, 5th Edition, 2001*
Ganciclovir
Ganciclovir Evaluation in Congenital CMV
Conduct of Study

Congenital CMV (culture proven) With CNS Involvement

Informed Consent

Ganciclovir vs. No Treatment x 42 days 12 mg/kg/day

Monitoring

Clinical/Virologic Serology Toxicity

Escape: Hematologic, Renal, Liver

Toxicity

Clinical Decline

Follow-up (Months 6, 12, 24, 36, 48, and 60)
Study Endpoints

- **Primary Endpoint**
  - Improved BSER by one gradation (or remains normal) between baseline and 6 month follow-up
    - Biologic assessment (total ears)
    - Functional assessment (best ear)

- **Second Endpoint**
  - Laboratory improvement by 2 weeks
  - Clinical improvement
Change in Hearing Between Birth and $\geq$ 1 Year of Age

Ganciclovir Recipients
- 79% Improved or Unchanged
- 21%* Worse

No Treatment Group
- 68% Improved or Unchanged
- 32% Worse

* 25 dB

P < 0.01

† > 30.6 dB

J Pediatric 2003;143:16-25
Development of Neutropenia During Therapy

Treatment adjustments 14/29 (48%)
- Dose adjusted 3
- Stopped and restarted 7
- Permanently stopped 4
## Average Total Delays Per Subject

<table>
<thead>
<tr>
<th>Follow-up Interval</th>
<th>Treatment (mean ± SE)</th>
<th>No Treatment (mean ± SE)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 weeks</td>
<td>1.5 ± 0.27</td>
<td>2.05 ± 0.27</td>
<td>0.13</td>
</tr>
<tr>
<td>6 months</td>
<td>4.46 ± 0.74</td>
<td>7.51 ± 1.00</td>
<td>0.06</td>
</tr>
<tr>
<td>12 months</td>
<td>9.78 ± 1.65</td>
<td>17.14 ± 1.93</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Sarah Oliver, J. Clin Virology, 2009
Average Total Delays Per Subject

- No Treatment
- Ganciclovir Treatment

P = 0.06
P = 0.007
## Average Total Delays Without Language

<table>
<thead>
<tr>
<th>Follow-up Interval</th>
<th>Treatment (mean ± SE)</th>
<th>No Treatment (mean ± SE)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 weeks</td>
<td>0.79 ± 0.18</td>
<td>1.23 ± 0.19</td>
<td>0.07</td>
</tr>
<tr>
<td>6 months</td>
<td>4.20 ± 0.65</td>
<td>6.56 ± 0.85</td>
<td>0.08</td>
</tr>
<tr>
<td>12 months</td>
<td>8.35 ± 1.46</td>
<td>15.03 ± 1.68</td>
<td>0.005</td>
</tr>
</tbody>
</table>
Average Total Delays

Without Language

- No Treatment
- Ganciclovir Treatment

P = 0.08
P = 0.005
Can We Use Valganciclovir?
Pro-Drug of Ganciclovir

Prodrug structure:

\[ \text{Prodrug} \]

\[ \text{HCl} \]

\[ \text{Ganciclovir} \]

Ganciclovir structure:
6 Weeks versus 6 Months of Oral Valganciclovir
Schematic of Study Design

Valganciclovir vs. placebo to complete 6 mos of total therapy
F/U weekly x 4 wks, then every two weeks x 8 wks, then every month x 3 mos

Oral valganciclovir

Oral placebo

6 wks of valganciclovir therapy

F/U at 1 yr
F/U at 2 yr
F/U at 7 mos
6 mos D/C study medication

Enrollment
Randomization

ABR

ABR

ABR Bayley III

ABR Bayley III

No treatment

No treatment

Bayley III

Bayley III
Oral Valganciclovir: Change in Hearing Between Birth and 12 Months

6 Weeks of Treatment
- 57% Improved or Remained Normal
- 43% Worse or Remained Abnormal

6 Months of Treatment
- 73% Improved or Remained Normal
- 27% Worse or Remained Abnormal

P = 0.01

aOR (95% CI): 3.34 (1.31, 8.53)

n=77 ears
n=79 ears
Oral Valganciclovir: Change in Hearing Between Birth and 24 Months

6 Weeks of Treatment

- 64% Normal
- 36% Worse or Remained Abnormal

n=58 ears

6 Months of Treatment

- 77% Normal
- 23% Worse or Remained Abnormal

n=70 ears

P = 0.04

aOR (95% CI): 2.66 (1.02, 6.91)
## Bayley III Developmental Scale
### Qualitative Descriptors of Composite Scores

<table>
<thead>
<tr>
<th>Composite</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>130 and above</td>
<td>Very superior</td>
</tr>
<tr>
<td>120-129</td>
<td>Superior</td>
</tr>
<tr>
<td>110-119</td>
<td>High average</td>
</tr>
<tr>
<td>90-109</td>
<td>Average</td>
</tr>
<tr>
<td>80-89</td>
<td>Low average</td>
</tr>
<tr>
<td>70-79</td>
<td>Borderline</td>
</tr>
<tr>
<td>69 and below</td>
<td>Extremely low</td>
</tr>
</tbody>
</table>
# 6 Weeks vs. 6 Months Oral Valganciclovir
Bayley III Developmental 24 Mo Outcomes

<table>
<thead>
<tr>
<th></th>
<th>6 Month Therapy</th>
<th>6 Week Therapy</th>
<th>Adjusted P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive Composite</td>
<td>89.6 ± 3.0</td>
<td>79.5 ± 2.8</td>
<td>0.0128</td>
</tr>
<tr>
<td>Language Composite</td>
<td>87.6 ± 3.0</td>
<td>76.8 ± 2.9</td>
<td>0.0090</td>
</tr>
<tr>
<td>Receptive Communication Scale</td>
<td>7.5 ± 0.5</td>
<td>6.1 ± 0.5</td>
<td>0.0544</td>
</tr>
<tr>
<td>Expressive Communication Scale</td>
<td>8.0 ± 0.5</td>
<td>6.5 ± 0.5</td>
<td>0.0224</td>
</tr>
<tr>
<td>Motor Composite</td>
<td>82.6 ± 3.2</td>
<td>73.2 ± 3.0</td>
<td>0.0289</td>
</tr>
<tr>
<td>Fine Motor Scale</td>
<td>7.3 ± 0.6</td>
<td>6.0 ± 0.6</td>
<td>0.1132</td>
</tr>
<tr>
<td>Gross Motor Scale</td>
<td>6.7 ± 0.5</td>
<td>5.4 ± 0.5</td>
<td>0.0672</td>
</tr>
</tbody>
</table>
# 6 Weeks vs. 6 Months Oral Valganciclovir Bayley III Developmental 24 Mo Outcomes

<table>
<thead>
<tr>
<th></th>
<th>6 Month Therapy</th>
<th>6 Week Therapy</th>
<th>Adjusted P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive Composite</td>
<td>Average</td>
<td>Borderline</td>
<td>0.0236</td>
</tr>
<tr>
<td>Language Composite</td>
<td>Average</td>
<td>Borderline</td>
<td>0.0037</td>
</tr>
<tr>
<td>Receptive Communication Scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expressive Communication Scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor Composite</td>
<td>Average</td>
<td>Borderline</td>
<td>0.0130</td>
</tr>
<tr>
<td>Fine Motor Scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gross Motor Scale</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Conclusions: 6 Weeks vs.. 6 Months of Oral Valganciclovir

- 6 months of oral valganciclovir therapy is superior to 6 weeks of therapy in subjects with symptomatic congenital CMV disease
  - Improved audiologic outcomes at 12 and 24 months
  - Improved communicative neurodevelopmental outcomes at 24 months
- Neutropenia is less common with longer-term oral valganciclovir than with IV ganciclovir
2017: Where Are We Now?

- Neonatal HSV Infection
  - Mortality reduced from 75% to 13%
  - Morbidity reduced from 90% to 30%
  - Suppressive Therapy Improves Long Term Morbidity

- Congenital CMV Infection
  - Mortality reduced from 15% to <1%
  - Morbidity reduced from 25% to <5%
  - Both Hearing and Developmental Outcome Improved with 6 months of valganciclovir Therapy

Savings to health care of >$5 billion annually
Conclusions:
Neonatal HSV Versus Congenital CMV Infections

• Yes, we improved morbidity and mortality with therapy for both diseases
• But, we need to do better:
  – Vaccines would be ideal but are a long way from reality
  – Combination therapy is the next best logical step, especially with the development of drugs having a different mechanism of action (pretilovir, letermovir, amenamevir, brincidofovir)
• Need to define biomarkers that predict progressive disease (e.g. asymptomatic congenital CMV infection)
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