Neonatal treatment for CMV: The Good the Bad and the Ugly
Congenital Cytomegalovirus Treatment

- Who?
- What?
- Where?
- When?
- Why?
Congenital CMV Infection

WHY?

• Most common congenital infection in developed world – 0.7% all births (meta-analysis, Dollard 2007)
• 25% of all SNHL at 4 years of age (Morton & Nance NEJM 2006)
• 40-58% profound SNHL (Dollard, 2007)
• Only potentially treatable cause of SNHL
Congenital CMV Infection

WHY?

~1,000 newborns with congenital CMV infection in each setting

127 symptomatic newborns (12.7%)

5 deaths (4%) and 122 survivors

50–70 children with permanent sequelae (45–58%)

61 children with motor/cognitive deficit (50%)

61 children with hearing loss (50%)

27 children with vision impairment (22%)

873 asymptomatic newborns (87.3%)

No deaths

118 children with permanent sequelae* (13.5%)

96 children with hearing loss (11%)

Number with motor/cognitive deficit not known

Number with vision impairment not known

2/3 of children with CMV hearing loss are in ‘Asymptomatic’ group at birth

Manicklal Clin Mic Rev 2013
## Symptomatic Congenital CMV - Clinical Findings At Birth

### CLINICAL
- **IUGR**: 26-43%
- **Microcephaly**: 20-53%
- **Hepato-splenomegaly**: 45-70%
- **Petechiae**: 45-75%
- **Jaundice**: 41-70%
- **Chorioretinitis**: 14-17%
- **Seizures**: 7-13%
- **Other neurological abnormalities**: 19-37%
- **Dental enamel defects**: 11%

### LABORATORY:
- **Thrombocytopenia**: 50-77%
- **Anaemia**: 7.0%
- **Raised ALT/AST**: 48-83%
- **Conjugated hyperbilirubinaemia**: 47-81%
- **CSF abnormalities**: 46%

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*From:*
- Kylat, Eur J Ped 2006
- Boppana, PIDJ 1992
- Noyola, J Ped 2001
Congenital CMV Infection

WHY?

- Prevent SNHL
- Prevent neurodevelopmental delay
- Prevent mortality?
- Treatment of liver disease?
Ganciclovir / Valganciclovir
■ Foscarnet
■ Cidofovir
■ Brincidofovir (CMX001, Chimerix, experimental)
■ Maribavir (ViroPharma, experimental)
■ Letermovir (AIC246, AiCuris/Merck, experimental)
■ Cyclopropavir (Microbiotix, experimental)
Congenital CMV Infection

WHO?

- 37/40
- BWt 1.5kg (0.4\textsuperscript{th} Centile)
- Petechiae, Plt 80
- Cr USS calcification
- Ventricular dilatation
EVIDENCE FOR TREATMENT - CNS?
- Collaborative Antiviral study group (CASG)
Kimberlin et al J Ped 2003;143: 16-25

- Inclusion: < 1 month of age with symptomatic CMV (“clinically apparent”) involving the CNS:
  - 1) Microcephaly
  - 2) Intracranial calcifications
  - 3) Abnormal CSF for age
  - 4) Chorioretinitis
  - 5) Hearing deficits

- EXCLUDED <32/40 and <1200g

- Randomised NOT placebo-controlled to receive 6 weeks treatment with IV Ganciclovir (GCV) 6mg/kg bid
Change in Hearing Between Birth and ≥ 1 Year of Age (Best Ear)

Ganciclovir Recipients

- 79% Improved or Unchanged
- 21% Worse

* 25 dB

P < 0.01

No Treatment Group

- 32% Improved or Unchanged
- 68% Worse

† > 30.6 dB

Kimberlin et al, J Pediatr 2003;143:16-25
CAGS Phase III Ganciclovir Study
- Average Total Delays using Denver Scale
  (Without Language)
N = 74 at 6 wks; 74 at 6 mths; 71 at 12 mths

![Graph showing average total delays for No Treatment and Ganciclovir Treatment over 6 weeks, 6 months, and 12 months. The graph indicates a statistical significance at P = 0.005 for Ganciclovir Treatment compared to No Treatment at 12 months.]

P = 0.005
P = 0.03
Oliver, J Clin Virol 2009
Treatment benefits and cautions

**OTHER BENEFITS**

- GCV group
  - Better weight gain and growth in head circumference @ 6wks
  - More rapid resolution of LFTs (19 days vs 66 P=0.03)

**CAUTIONS**

- Only 43/100 hearing evaluable at ≥ 1 years
- 8 patients with chorioretinitis no difference in resolution between treated and untreated (P=0.23)

**Toxicity**
- Grade 3/4 neutropenia 63% GCV (vs 21% control P <0.01)
- Prolonged IV access necessary (3 line infections during study 1 GNS)
- Theoretical long-term risks (gonadal toxicity, carcinogenicity)
Congenital CMV Infection
WHO?

- 37/40
- BWt 1.7kg (0.4\textsuperscript{th} Centile)
- Petechiae – Plt 90
- Hepatosplenomegaly (3cm palpable)
- Normal liver function
PREDICTING LONG-TERM SEQUELAE

- Petechiae, IUGR independent risk factors for hearing loss (Rivera 2002)
- Thrombocytopenia risk for neurocognitive impairment (Blazquez, Abstract CMV conf San Francisco 2012)
- Poor outcome seen if abnormal BAER (Kylat, 2006)

- Undetectable viral load good negative predictive value (Rivera 2002, Boppana 2005, Ross 2009)
ANY SYMPTOMATIC CONGENITAL CMV
<30 days; ≥32/40 GA; >1800g

SYMPTOMATIC
CCMV
Thrombocytopenia, petechiae, HSM, hepatitis, SGA, CNS,

RANDOMISATION
6 wks oral VGCV 16mg/kg bd as standard
(shown equiv. to IV GCV 6mg/kg/day – Acosta, Clin Pharmacol & Therapeut 2007)

Complete 6 month course with oral VGCV
Complete 6 month course with placebo

1º outcome: Change in hearing baseline vs 6/12
2º outcome: Toxicity
12,24 mnth hearing outcome
12 month neurological outcome
No baby enrolled had isolated SNHL
### Table 2. Improvement and Protection in Best-Ear and Total-Ear Hearing between Baseline and Follow-up.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>No. of Participants or Ears</th>
<th>Comparison of Hearing at Baseline and Follow-up</th>
<th>Unadjusted Analysis</th>
<th>Adjusted Analysis</th>
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<tbody>
<tr>
<td></td>
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<td>Improved Hearing at Follow-up</td>
<td>Normal Hearing at Baseline and Follow-up</td>
<td>Same Degree of Hearing Loss at Baseline and Follow-up</td>
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<td>Primary analysis: best ear</td>
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<td>6-Mo group</td>
<td>43</td>
<td>2 (5)</td>
<td>28 (65)</td>
<td>8 (19)</td>
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<td>6-Wk group</td>
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<td>3 (7)</td>
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<td>14 (33)</td>
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<td>6-Mo group</td>
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<td>6 (7)</td>
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<tr>
<td>6-Wk group</td>
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<td>7 (8)</td>
<td>39 (46)</td>
<td>29 (35)</td>
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<td>12-Mo analyses</td>
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<tr>
<td>Best ear</td>
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<tr>
<td>6-Mo group</td>
<td>41</td>
<td>2 (5)</td>
<td>30 (73)</td>
<td>6 (15)</td>
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<tr>
<td>6-Wk group</td>
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<td>2 (5)</td>
<td>23 (58)</td>
<td>10 (25)</td>
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<tr>
<td>Total ears</td>
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<td></td>
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<td>6-Mo group</td>
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<td>52 (66)</td>
<td>15 (19)</td>
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<td>6-Wk group</td>
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<tr>
<td>Best ear</td>
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<tr>
<td>6-Mo group</td>
<td>37</td>
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<td>30 (81)</td>
<td>2 (5)</td>
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<td>6-Wk group</td>
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<td>3 (6)</td>
<td>20 (65)</td>
<td>7 (23)</td>
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<td>Total ears</td>
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<td>6-Mo group</td>
<td>70</td>
<td>6 (9)</td>
<td>48 (69)</td>
<td>8 (11)</td>
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<td>6-Wk group</td>
<td>58</td>
<td>2 (3)</td>
<td>35 (60)</td>
<td>16 (28)</td>
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</table>
Change in hearing between birth and 12 mo (best ears)

Valganciclovir 6 weeks:
- Improved or normal: 63%
- Worse or remained abnormal: 37%

Valganciclovir 6 months:
- Improved or normal: 78%
- Worse or remained abnormal: 22%

GCV 2003:
- Improved or normal: 50%
- Worse or remained abnormal: 50%
Benefits of treating for 6 months?

- Subjects with CNS involvement at baseline have a 46% greater likelihood of better outcome at 24 months if receiving 6 month treatment compared to 6 weeks (19% in those without CNS disease)

- Only significantly better for total ear analysis and once baseline CNS adjusted for.

- Improved language and receptive-communication outcomes in 6 month group
- Trend toward better outcomes in all other neurocognitive areas but Not significant (Bonferroni adjustment applied – sig = p value <0.0071)
- No difference in neurodevelopment in CNS vs no CNS involvement
Ganciclovir/valganciclovir

- **SIDE EFFECTS**
  - Bone marrow suppression
  - Neutropenia
  - Hepatotoxicity
  - Gastrointestinal (ValGCV)
  - Neurological (adults with renal impairment)
  - Potential for
    - Gonadotoxicity (animal models)
    - Carcinogenicity (animal models)

Congenital CMV – Where?
At home with monitoring from a centre that can monitor Side effects

Gwee, PIDJ, 2014
<table>
<thead>
<tr>
<th>Treatment received</th>
<th>GCV 6 wks</th>
<th>ValGCV + GCV (dosing)</th>
<th>ValGCV D1-42</th>
<th>ValGCV total 6 mo</th>
<th>ValGCV total 6 week</th>
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<tbody>
<tr>
<td>No treatment</td>
<td>Treatment</td>
<td></td>
<td></td>
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<tr>
<td>Total grade 3-4</td>
<td>9 (20.9%)</td>
<td>29 (63.0%)</td>
<td>9 (37.5%)</td>
<td>21 (19.3%)</td>
<td>13 (26.5%)*</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>10 (21.3%)*</td>
</tr>
</tbody>
</table>

*P=>0.6

Valganciclovir seem to cause less neutropenia than GCV
Toxicity does not seem problematic in longer treatment courses
47 children enrolled in CASG #102 (study of ganciclovir) as neonates

No adverse effects noted in relation to cancer incidence, sexual development or pubertal development (unpublished).

NO published long-term follow-up data
St George's University of London

Congenital CMV Infection

WHO?

- 37/40
- BWt 2.6kg
- Plt 110

Sensorineural hearing loss on routine screening

Unilateral hearing loss left side confirmed age 30 days
No babies in either RCT had isolated SNHL
Most babies had multiple clinical abnormalities

- Dreher et al J Ped 2014
- Multiple clinical abnormalities more likely to have sequelae than those with isolated findings (53% vs 31% p=0.02) (Dreher, J Ped 2014)
- Isolated petechiae 20% SNHL similar to SNHL in ‘asymptomatic’ group (Dahle 2000)
- CONCERT 2 – Leiden (NCT02005822) study of valGCV in babies presenting through NHSP vs historical controls
Who to treat – European consensus

CNS – as defined in studies
YES, treat
6 months treatment
Life and sight threatening disease or sig organ disease

SNHL – isolated
Yes but NOT CONSENSUS
?6 months treatment justified
CONCERT study NCT02005822

Well baby with no CNS disease or notable organ disease
Isolated or transient findings
NO but discuss on case by case basis
If treat ?6 months
Summary

WHO:  - Babies with CNS disease
   – Not fully defined: Calcification, ventriculomegaly, sig white matter disease
   – CNS not routinely carried out
   – Babies with life or site threatening disease (or multiorgan involvement)
   – NOT babies without symptoms or minor, transient findings

WHAT:  - Ganciclovir or Valganciclovir if tolerated

WHERE: - Out-patient if baby well

WHEN:  - < 1 month

WHY:  - Prevent hearing deterioration, neurological impairment
   - possibly more rapid resolution of abnormal LFTs
SUMMARY

- GOOD - Treating babies with CNS disease leads to improved hearing outcomes
  - Treatment effect modest with 6 months compared to 6 weeks and only for total ear (not best ear hearing)
  - Treating babies with symptomatic CMV improves neurological outcomes (language)

- BAD - Side effects generally well tolerated
  - No monitoring of long-term sequelae

- UGLY - Evidence lacking for treatment in non-CNS groups – but happening
  - Evidence lacking for defining CNS disease with newer neuroimaging
  - Evidence lacking for treating isolated SNHL (trials in progress).
WORK TO BE DONE

- More clearly define significant CNS disease, ‘disease scoring’
- More clearly define groups in whom treatment gives benefit (or not)
  - RCTs
  - Epidemiological follow-up and data (Disease Registries)
- Enable long term monitoring of toxicity (Disease Registries)
- Define/develop biomarkers of treatment efficacy
- European Congenital CMV Initiative Registry