Neonatal Herpesvirus Infections: Benefits of Collaborative Trials

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Division of Immunology & Infectious Disease

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Disclosure

- I disclose the following relationships with commercial companies:
  - I am on the Speakers' Bureau for: Merck & Co., Inc., Sanofi Pasteur, Novartis, MedImmune.
  - I am on the Advisory Board for: Novartis.

OUTLINE

- Background: Neonatal Herpesvirus Infections
  - HSV
  - CMV
- What is the Collaborative Antiviral Study Group (CASG)?
- Neonatal HSV: Evolution of Treatment and Suppression Studies
- Congenital CMV: Antiviral Trials – Progress
- Summary

Neonatal Herpes Simplex Virus (HSV) Infections

- Caused by HSV-1 or HSV-2
- 1st infection → High rate of transmission to infant (50%)
- Most infections transmitted via reactivation in a previously infected mom
- Symptoms begin 1 to 5 weeks after birth

Classification of Neonatal Herpes Based on Time of Transmission

Perinatal Herpes Classification

- % of Total
  - Skin, Eye, Mouth: 40%
  - CNS: 35%
  - Disseminated: 25%
SEM Disease*

- **Age at presentation:** 10 - 12 days
- **Most common manifestations**
  - Skin vesicles 83%
  - Lethargy 19%
  - Conjunctivitis 25%
  - Fever 17%
- **Untreated:**
  - 70% can progress to CNS/disseminated disease
  - 50% recurrence of skin lesions over 6 mos
- **With ACV treatment:**
  - Zero mortality
  - Low morbidity (2%)

*Kimberlin et al. (CASG) Pediatrics 2001;108:223-9

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CNS disease*

- **Older presentation:** 15 - 17 days
- **Common presenting manifestations**
  - Skin vesicles 63%
  - Seizures 57% (focal)
  - Lethargy 49%
  - Fever 44%
- **With acyclovir treatment**
  - Low mortality (6%)
  - High morbidity (70%)

*Kimberlin et al. (CASG) Pediatrics 2001;108:223-9

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Disseminated Disease*

- **Age at presentation:** 9-12 days
- **Presenting manifestations**
  - Skin vesicles 58%
  - Fever 56%
  - Lethargy 47%
  - Pneumonia 37%
  - DIC 34%
- **Highest rate of mortality (30%)** despite treatment

*Kimberlin et al. (CASG) Pediatrics 2001;108:223-9

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CONGENITAL CMV DISEASE

**Congenital CMV: Overview**

- CMV is the most common...
  - congenital infection
  - non-heritable cause of sensorineural hearing loss in children
  - infectious cause of brain damage in U.S. children

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Morbidity & Mortality for 3 Groups of Neonates Treated with Acyclovir

- **Mortality**
  - SEM (9 at 24 mos)
  - CNS (8 at 12 mos)
  - Disseminated (1 at 12 mos)

Maternal Immunity and Congenital CMV Infection

Pregnant women

Adapted from Adler SP, “Intrauterine Infections” In: Pediatric Infectious Diseases: Principles & Practice (Jenson, Baltimore – eds) 2002

<table>
<thead>
<tr>
<th>Immune (40-80%)</th>
<th>Non-Immune (20-60%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No congenital CMV infection (98-99.5%)</td>
<td></td>
</tr>
<tr>
<td>Congenital CMV infection (0.5-2%)</td>
<td></td>
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<tr>
<td>1-4% acquire 1st CMV infection</td>
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<tr>
<td>40% transmit CMV to fetus</td>
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<tr>
<td>33% infected fetuses develop disease</td>
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</table>

Findings in Symptomatic Congenital CMV Infections*

- 86% (91/106) have at least 2 of the following:
  - Petechiae
  - Jaundice
  - Hepatosplenomegaly
  - Microcephaly
  - Seizures
  - Hearing loss, other neurologic signs
- 14% (15/106) have only one manifestation
  - Petechiae
  - Jaundice
  - Microcephaly
  - HSM, hydrocephalus, hypotonia


The Collaborative Antiviral Study Group (CASG)

- In existence since 1972
- Funded by National Institutes of Health/National Institute of Allergy & Infectious Diseases
- Investigators from U.S., Canada, U.K. and Sweden
- Conducts collaborative studies of antiviral therapy for herpesvirus infections (initially), and now also other infections (e.g., enterovirus, hepatitis, influenza) in newborns, children, and adults

The CASG (continued)

- Principal Investigator:
  - Richard Whitley (University of Alabama [UAB])
- Co-PI:
  - David Kimberlin (UAB)

INITIAL NEONATAL HERPES TRIALS CONDUCTED BY CASG
Two Landmark CASG Neonatal HSV Studies

- Vidarabine vs Placebo Trial\(^1\) (N=56)
  - Efficacy shown earlier in adults with HSV encephalitis
  - Mortality for (CNS+Disseminated) groups lowered: 74% → 38%
  - Mortality for isolated CNS disease: 50% → 10%

- Acyclovir vs. Vidarabine\(^2\) (N=202)
  - Drugs w/ comparable efficacy, minimal adverse effects
    - Vidarabine given as 12-hour infusion once/day
    - Acyclovir given over 1 hr.
  - “…we recommend acyclovir as the treatment of choice in a dosage of 30 mg/kg/d for 10 days.”

Neonatal HSV Trials: Shift to Suppression Studies

- Earlier publication\(^1\) described 5 neonates with CNS herpes, examined retrospectively
  - All treated with IV acyclovir or vidarabine
  - At one month:
    - 3 infants - persistent CSF abnormalities, and severe neurologic sequelae (no suppressive antiviral after IV course)
    - Other 2 infants - CSF normal, only mild neurologic deficits (both suppressed with oral ACV x 3-12 mos)

- Q: Could long term suppression with oral acyclovir reduce neurologic sequelae in survivors after IV ACV therapy?

Phase III Suppression Trial for Neonatal Herpes\(^1\)

- Infants with all forms of disease enrolled
- Receive standard 21d course of IV acyclovir
- Within 12 hrs of completing IV acyclovir…
- Start suppressive treatment:
  - 6 months of po acyclovir, 300 mg/m\(^2\)/dose given 3x/d
  - Skin recurrences treated with open label oral ACV
- Careful followup (2.4 wks; 2.3,4.5,6 mos; 1 yr)
  - 1\(^{st}\) endpoint: developmental testing at 12 months (Bayley Scales of Infant Development)

Higher Dose Acyclovir

- Acyclovir: “High dose” (60 mg/kg/d) vs standard dose\(^1\) (N=69)
  - Lower mortality overall, and in disseminated dz group
  - Self-reversible neutropenia in 6 patients
  - High dose acyclovir x 21 days (14 days for SEM) became accepted for treatment of neonatal herpes

- But…
  - Morbidity remained unacceptably high for survivors of CNS disease (20%)\(^1\)
  - Increased # skin recurrences after SEM disease associated w/ 20% rate of neurologic sequelae\(^2\)

Phase I/II Trial (1989-92)\(^1\)

- Conducted in preparation for large Phase III (efficacy) trial
- Neonates (N=26) w/ SEM herpes
- Acyclovir dose: 300 mg/m\(^2\)/dose po, 2 - 3 x/day x 6 mos
- Drug Toxicity: 12/28 (46%) w/ neutropenia (resolved spontaneously in 10 infants)
- Results: Viral suppression
  - 19% on 3x/day dosing had skin recurrences during 6 months (historical controls w/ no therapy: 46% recurrences)
- CSF reactivation of HSV occurred in one of the 3 infants with skin recurrence

Time to Discontinuation of Study Drug

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Months Receiving Drug</th>
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<tbody>
<tr>
<td>Acyclovir</td>
<td>24</td>
</tr>
<tr>
<td>Placebo</td>
<td>21</td>
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Pediatrics Grand Rounds
07 September 2012

Time to Discontinuation of Study Drug

Summary: Oral Acyclovir Suppression after Neonatal Herpes

- Developmental outcome* (at 12 mos)
  - Infants w/ CNS disease, receiving ACV: higher mean scores vs. placebo recipients (scores 88.24 vs 68.12)
  - Acyclovir decreases # of cutaneous recurrences
  - Trend for higher rates of neutropenia in ACV recipients, but not significant (p=.09)
    - WBCs recovered in all cases (some w/ temporary drug cessation)
    - No complications of neutropenia
    - No other adverse laboratory events associated w/ ACV
    - No adverse events led to discontinuation of study drug


Ganciclovir for Congenital CMV: Results of a CASG Trial*

- 100 neonates with symptomatic congenital CMV infection involving CNS
- 6 weeks IV ganciclovir vs. no treatment
- Results
  - Less hearing deterioration at 6, 12 months in ganciclovir group
  - Frequent neutropenia in ganciclovir recipients (63%) vs. controls (21%)
  - No effect on mortality

*Kimberlin DW et al., J Pediatr 2003;143:16-25

CONGENITAL CMV TREATMENT TRIALS

Followup Study: Focusing on Neurodevelopmental Outcome†

- Utilized same 100 patients with congenital CMV involving CNS (6 wks IV GCV vs. no treatment)
- Performed Denver II Developmental Screening Test at 6 wks, 6 mos, 12 mos (Examiners could not be blinded)
- Significant benefit with receipt of GCV:
  - At 12 mos: 10.1 vs 17.1 milestone delays (GCV vs no treatment, respectively)
  - Multivariate regression model: benefit of GCV remained significant
- Criticism: use of a screening test to assess development

†Oliver SE, et al., J Clin Virol 2009;465:S22-S26

Note: study underpowered for detecting actual differences in neutropenia rates

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2Note: study underpowered for detecting actual differences in neutropenia rates
Total Delays on DDST at 3 Time Points

(A) All 4 components of test

(B) Only 3 components (exclude Language)

CASG: Other Recent Protocols

- **Influenza**
  - PK/PD Study of Oseltamivir in infants: retrospective chart review at selected institutions to assess safety in infants
  - Data used by CDC to document compassionate use of oseltamivir in infants for pandemic flu
  - Investigation of IV peramivir in children with influenza who fail or do not tolerate standard drugs

- **Enterovirus**
  - Pleconaril for enterovirus sepsis syndrome in neonates

**Neonatal Herpesvirus Infections: Benefits of Collaborative Trials**

- Neonatal herpes and congenital CMV are rare
- Proper conduct of randomized trials requires strong leadership and collaborations among multiple investigators at specialized clinical research centers
- The CASG has a long tradition of success in treating viral infections in neonates
- Trials may take a decade to complete

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"Good things come to those who wait"