

Oral Acyclovir Aids Neurodevelopment in HSV

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VANCOUVER, B.C. – Treating infants with herpes simplex virus infectious who have central nervous system involvement with 6 months of oral acyclovir improved neurodevelopmental outcomes at 1 year, according to findings from two phase III, double-blind, placebo-controlled studies.

Achieving prolonged antiviral suppression also prevented recurrence of HSV skin lesions, said Dr. David Kimberlin.

Following the usual course of intravenous acyclovir therapy for neonatal CNS or skin-eye-mouth herpes simplex virus (HSV) disease, “our data strongly support that [infants] should then be started on 6 months of oral acyclovir



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DR. KIMBERLIN

suppressive therapy, with periodic monitoring of [their] white blood cell counts,” said Dr. Kimberlin, a pediatric infectious disease specialist at the University of Alabama at Birmingham.

“This is a very important advance” that is “expected to change clinical practice involving babies who are diagnosed with neonatal HSV,” said Dr. Anne Gershon, director of the division of pediatric infectious disease at Columbia University Medical Center, New York. Dr. Gershon was not involved in the studies.

The trials ran concurrently from 1997 to 2008, and were conducted by the National Institute of Allergy and Infectious Diseases’ Collaborative Antiviral Study Group.

In the first study, 24 infants with herpes simplex virus CNS disease were randomized to acyclovir suppression at 300 mg/m² per dose orally 3 times daily for 6 months; 21 were randomized to placebo. Treatment came immediately after the infants completed a 2- to 3-week course of intravenous acyclovir, with polymerase chain reaction confirmation that the virus had been cleared from their spinal fluid.

In the second study, following parenteral therapy, 15 infants with skin-eye-mouth (SEM) HSV disease were randomized to the same dosage of oral acyclovir; 14 to placebo.

In both studies, children who developed blisters or other HSV skin manifestations were taken off their blinded intervention and treated with open-label acyclovir; following resolution, the blinded interventions were resumed. After a second skin recurrence, however, the blinded intervention was halted and infants were allowed to be switched to the acyclovir suppression regimen.

Because of skin eruptions, only eight infants in the CNS study and four in the SEM study completed 6 months of blinded placebo. Others in the placebo groups “ended up getting suppressive therapy but for something less than 6 months,” Dr. Kimberlin said.

Baseline demographics were balanced between the placebo and acyclovir groups, except that babies randomized to acyclovir in the CNS study were smaller

at delivery and lighter at the time of enrollment than were those randomized to placebo; acyclovir-treated babies in the SEM study were lighter at enrollment, as well, he said.

At 12-month follow-up, after adjustment for covariates, children in the CNS study randomized to acyclovir had significantly higher mean mental scores on the Bayley Scales of Infant Development, second edition, compared with subjects

on placebo (88.24 vs. 68.12, $P = .046$).

A Bayley score of 100 represents the mean mental score, with a standard deviation of plus or minus 15; a score below 70 is 2 standard deviations below the mean (Pediatrics 2005;116:123-9).

“For the group randomized to immediate suppressive therapy, 60% of them had normal development at 12 months of age. In contrast, [in] the group randomized to placebo, about 30% of them



Select safety information

RotaTeq is indicated for the prevention of rotavirus gastroenteritis in infants and children caused by the serotypes G1, G2, G3, and G4 when administered as a 3-dose series to infants between the ages of 6 to 32 weeks.

The vaccination series consists of 3 ready-to-use liquid doses of RotaTeq administered orally starting at 6 to 12 weeks of age, with the subsequent doses administered at 4- to 10-week intervals. The third dose should not be given after 32 weeks of age.

RotaTeq should not be administered to infants with a demonstrated history of hypersensitivity to the vaccine or any component of the vaccine.

Infants with Severe Combined Immunodeficiency Disease (SCID) should not receive RotaTeq. Post-marketing reports of gastroenteritis, including severe diarrhea and prolonged shedding of vaccine virus, have been reported in infants who were administered RotaTeq and later identified as having SCID.

No safety or efficacy data are available from clinical trials regarding the administration of RotaTeq to infants who are potentially immunocompromised.

No safety or efficacy data are available for administration of RotaTeq to infants with a history of gastrointestinal disorders.



VITALS

Major Finding: HSV-infected infants with CNS involvement who were randomized to 6 months of oral acyclovir suppression following initial parenteral therapy had significantly higher mean mental scores on the Bayley Scales of Infant Development, compared with infants randomized to placebo (88.24 vs. 68.12, P value .046).

Data Source: Two phase III, double-blind, placebo-controlled trials enrolling a total of 74 infants.

Disclosures: The studies were funded by the National Institutes of Health. Dr. Kimberlin said he has no conflicts of interest. Dr. Gershon reported that she is a Merck grant investigator and scientific adviser to GlaxoSmithKline.

had normal development at 12 months of age," Dr. Kimberlin said.

Longer durations of acyclovir treat-

ment correlated with higher Bayley scores in infants treated with acyclovir for less than 6 months.

In both the SEM and CNS trials, acyclovir delayed HSV skin recurrences by more than 2 months (P value .009).

Dr. Kimberlin and his colleagues were concerned at the outset of the trials that prolonged acyclovir suppression would lead to neutropenia, but "we fortunately saw much less of that than we anticipated we might," he said.

Overall, incidence and degree of neutropenia were not different between the acyclovir and placebo groups (CNS, $P = .94$; SEM, $P = .24$).

However, absolute neutrophil counts of 500 cells/mm³ or less "occurred a

little bit more quickly among patients randomized to acyclovir than patients randomized to placebo. This was not statistically significant, but it did approach significance. We have to think that neutropenia at least may be related to prolonged oral acyclovir therapy," Dr. Kimberlin said.

There were no statistically significant differences in blood and chemistry labs and adverse events between the two groups. "The safety is much better than I feared it might be, and there is benefit, so benefit in my view outweighs risk," he said. ■

Multiple serotypes in one vaccine

RotaTeq is a rotavirus vaccine that contains multiple serotypes. It helps protect baby against rotavirus gastroenteritis caused by serotypes G1, G2, G3, and G4.

Select safety information (cont)

Vaccine virus transmission from vaccine recipient to non-vaccinated contacts has been reported. Caution is advised when considering whether to administer RotaTeq to individuals with immunodeficient contacts.

In clinical trials, the most common adverse events included diarrhea, vomiting, irritability, otitis media, nasopharyngitis, and bronchospasm.

In post-marketing experience, intussusception (including death) and Kawasaki disease have been reported in infants who have received RotaTeq.

RotaTeq may not protect all vaccine recipients against rotavirus.

Before administering RotaTeq, please read the adjacent Brief Summary of the Prescribing Information.

RotaTeq 

(Rotavirus Vaccine,
Live, Oral, Pentavalent)

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