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 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.

'The safety is much better than I feared it might be, and there is benefit, so benefit in my view outweighs risk.'

DR. KIMBERLIN

"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/m^2 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

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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.

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

Longer durations of acyclovir treatment 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/mm^3 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. ■