Telbivudine Appears Safe in Pregnancy

BY DIANA MAHONEY

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BOSTON – Limited use of the antiviral drug telbivudine is safe and effective for pregnant women with active hepatitis B virus infection and reduces perinatal transmission of the virus to their infants, Dr. Calvin Pan reported at the meeting.

In the first open-label case-control trial investigating the safety and efficacy of telbivudine during the second to third trimester of pregnancy, the synthetic nucleoside analogue led to significant increases in rates of complete virologic response and normalization of alanine aminotransferase (ALT) levels in treated vs. untreated pregnant women with hepatitis B virus (HBV) infection, reported Dr. Pan of Mount Sinai School of Medicine in New York.

The findings from this study suggest that limited treatment with telbivudine can improve maternal and child outcomes.

Additionally, there were no congenital defects identified up to 28 weeks post partum in the infants born to treated mothers.

Dr. Pan and his colleagues at the Second Affiliated Hospital of the Southeast University in Nanjing, China, where the study was conducted, enrolled 88 pregnant women who screened positive for hepatitis B e antigen (HBeAg) between gestational weeks 12 and 23 and who had serum HBV DNA levels greater than 6 $\log_{10}$ copies/mL and elevated ALT levels up to 10 times the upper limit of normal (40 IU/mL). Of the 88 patients, 53 opted to take telbivudine, and the remaining 35 served as the study's control arm, he said.

Women in the treatment arm received 600 mg/day of telbivudine beginning sometime between 20 and 32 weeks' gestation and continuing until a minimum of 4 weeks post partum, and infants born to women in both groups received hepatitis B immunoglobulin within 24 hours of birth and the HBV vaccine at birth, 1 month, and 6 months.

The mean duration of telbivudine treatment was 15.5 weeks, and all of the women who took the drug remained in the study through at least postpartum week 4, compared with 92% of the controls, said Dr. Pan. Physical and laboratory examinations were conducted at baseline, at the time of delivery, and at 4 weeks post partum, he said, noting that a second study looked at infant outcomes through 28 weeks.

At the time of delivery and 4 weeks post partum, a complete virologic response was observed in 53% and 62% of the treated patients, respectively, while no patients in the control arm achieved a complete virologic response at either time point, Dr. Pan reported. "Both the control arm and the telbivudine arm had HBV DNA of approximately 8 logs. At the time of delivery, this was reduced substantially [to 2.35 $\log_{10}$ copies/mL] in the mothers in the treatment arm."

With respect to ALT levels, 77% of the treatment group achieved normalization compared with 29% of the control group, Dr. Pan said. Also, the levels of HBeAg dropped by 98% in the treatment group, which was a significantly greater decrease than the 60% drop observed in the control group; the latter was likely the result of natural viral clearance, he noted.

An evaluation of newborn outcomes showed no congenital deformities nor any differences in gestational age, infant height and weight, or Apgar scores between the two groups, said Dr. Pan. Significantly fewer babies born to telbivudine-treated mothers vs. untreated mothers had hepatitis B surface antigens or detectable levels of HBV RNA at birth (4% vs. 23%).

Telbivudine appeared to be well tolerated as there were no adverse event–related treatment discontinuations, said Dr. Pan. Also, none of the patients experienced virologic breakthrough.

Despite concerns regarding antiviral treatment during pregnancy because of the potential risks to the fetus, the findings from this study suggest that limited treatment with telbivudine can improve maternal and child outcomes, Dr. Pan concluded.

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DRUGS, PREGNANCY, AND LACTATION

Treatment of Genital Herpes Simplex

Genital infections with herpes simplex virus (both HSV-1 and HSV-2) are among the most common sexually transmitted diseases. Although the true incidence of the infection in women is unknown, data from one large national study suggested that it is greater than 26% (Obstet. Gynecol. 2007;109:1489-98).

Treatment with antiviral drugs is indicated in pregnancy because both herpes types can infect the fetus (rarely) and newborn (commonly), resulting in significant morbidity and mortality. Primary infections have a higher risk of perinatal transmission than does recurrent infection.

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Primary infection close to delivery has the highest risk for fetal and neonatal complications. Intrauterine infection, although rare, can result in abortions or stillbirths, skin scars, ophthalmic complications (chorioretinitis, microphthalmia), and brain damage. In addition to death, neonatal infection may involve the skin, eyes, mouth, and central nervous system, and if disseminated, the liver, lung, brain, skin, and adrenals (Reprod. Toxicol. 2006;21:436-45).

Treatment of herpes in pregnancy usually involves either acyclovir or valacyclovir. A third agent, famciclovir, also is used but to a much lesser extent. For primary infection, a 7- to 10-day course (or longer if healing is incomplete) of acyclovir or valacyclovir is recommended, whereas a symptomatic recurrent episode should be treated for 5 days with either drug. Daily doses of either agent starting from 36 weeks' gestation are recommended for suppression (Obstet. Gynecol. 2007;109:1489-98). An advantage of valacyclovir is the twice daily dosing, compared with the three times daily dosing for acyclovir. However, for symptomatic recurrent episodes, daily doses of valacyclovir or acyclovir can be reduced to once or twice daily, respectively, by using higher-strength tablets.

There are a substantial amount of pregnancy data for acyclovir, most of which came from the Acyclovir in Pregnancy Registry. The prevalence of birth defects among registry cases was similar to the expected background risk, and there was no pattern among the defects suggesting a common cause. A 2009 review concluded that acyclovir was safe in pregnancy (Indian J. Dermatol. Venereol. Leprol. 2009;75:566-74).

There is far less pregnancy data for valacyclovir and famciclovir, raising questions about the risk of these antivirals. However, because valacyclovir is a prodrug that is converted in vivo to acyclovir, many believe it should be classified the same as acyclovir. A 2010 study provided more data, but the number of first-trimester valacyclovir exposures is still too limited to either confirm or refute this opinion.

In a population-based historical cohort study of all live-born infants in Denmark between 1996 and 2008, national registries were used to determine individual exposure to antiviral drugs, classification of birth defects observed within the first year of life, and potential confounders (JAMA 2010;304:859-66). Infants with chromosomal abnormalities, genetic syndromes, birth defect syndromes with known causes, or congenital viral infections were excluded from the analysis. Among 1,816 infants exposed during the first trimester to acyclovir, valacyclovir, or famciclovir, 40 (2.2%) had a major birth defect, compared with 19,920 (2.4%) among those not exposed, an insignificant difference.

For specific drugs, the number of birth defects and infants exposed in the first trimester were 32/1,561 for acyclovir (2.0%), 7/229 for valacyclovir (3.1%), and 1/26 for famciclovir (3.8%). The data for acyclovir and valacyclovir were nonsignificant, and the data for famciclovir were too small to analyze. The observed birth defects were classified into 13 subgroups: nervous system, eye, ear-face-neck, heart, respiratory, orofacial clefts, digestive system, abdominal wall, urinary, genital, limb, musculoskeletal, and miscellaneous. The percentage of cases in each defect category was statistically similar to that for nonexposed cases. Although the number of cases in each subgroup was small, there was no pattern between any first-trimester antiviral drug exposure and the different birth defects.

The authors of an accompanying editorial agreed that the data were reassuring in that these agents did not increase the overall risk of major defects (JAMA 2010;304:905-6). However, the question remained regarding whether these agents were associated with an increased risk of specific defects. Case-control studies will be needed to answer this question. Another limitation that was identified was use of a prescription database. As with all studies that use such databases, there is uncertainty whether the drug was actually taken, the dose taken, and when it was taken. Moreover, many defects are not recognized until after the first year of life, and these would have been missed by the study.

Famciclovir is a prodrug that is converted in vivo to penciclovir, the active antiviral agent. The animal data suggest low risk, but the human pregnancy experience is too limited to accurately assess the potential for embryo-fetal risk. In addition to the 26 cases described above, first-trimester exposure to famciclovir in six pregnancies was reported in a 1998 observational cohort study (Br. J. Obstet. Gynaecol. 1998;105:882-9). The outcomes included two spontaneous abortions and four normal, full-term infants. Although a risk assessment cannot be made with confidence based on human experience, if famciclovir is indicated it should not be withheld because of pregnancy. Both acyclovir and valacyclovir appear to be compatible with breastfeeding. However, there are no human data for famciclovir and, until such data are available, the drug is best avoided during breastfeeding.

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