VEMs Pose Possible Threat to Hepatitis B Control

Hepatitis B vaccine escape mutants are here, but how dangerous they will be is unknown.

BY BRUCE JANCIN

EXPERT ANALYSIS FROM A CONFERENCE ON PEDIATRIC INFECTIOUS DISEASES

VAIL, COLO. – The emergence of hepatitis B vaccine escape mutant viral strains poses a possible serious threat to the success of the global hepatitis B control program of the World Health Organization, although thus far the danger remains theoretical, according to Dr. Myron J. Levin.

"I think this is a potential crisis for us to keep track of," Dr. Levin explained at the conference, sponsored by the Children's Hospital, Denver.

Hepatitis B vaccine escape mutants (VEMs) are already here, and there is considerable selection pressure for the formation of more.

Under the wrong conditions, they are capable of causing breakthrough hepatitis B infection in fully immunized individuals.

VEMs occur most often in countries with high rates of endemic hepatitis B infection and universal hepatitis B vaccine immunization programs, such as Taiwan.

A recent report indicates that in the pre–vaccine era, 7.8% of Taiwanese patients with hepatitis B possessed mutant strains not recognized by the vaccine (Antivir. Ther. 2010;15:463-9).

Fifteen years after introduction of universal infant immunization in that country, the prevalence of VEMs among individuals with hepatitis B disease was close to 25%.

On a more positive note, while the prevalence of VEMs has indeed grown, the pool of Taiwanese with serious hepatitis B infection has shrunk markedly. Indeed, the rate of seropositivity to hepatitis B surface antigen (HBsAg) among Taiwanese children has decreased by 95% since the vaccine program was introduced. Liver cancer in this population has been reduced by 60%.

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"So the implication is right now there is no obvious problem. But it's something we need to monitor," observed Dr. Levin, professor of pediatrics and medicine at the University of Colorado, Denver.

Worst case scenario? The vaccines would have to be redesigned to recognize VEMs and incorporate hepatitis B virus proteins that aren't vulnerable to escape mutations, he added.

Selection pressure for formation of VEMs comes from two distinct sources: immunization and lamivudine monotherapy for chronic hepatitis B.

The hepatitis B virus is a DNA virus that utilizes a reverse transcriptase enzyme to replicate its viral genome, as does HIV. Reverse transcription is a notoriously error-prone process that can lead to single–amino acid mutations in HBsAg. The antibodies drawn forth by the hepatitis B vaccine specifically target the surface antigen protein. If the surface antigen protein contains a mutation, the vaccine may be unable to neutralize the virus, and a VEM is created.

Moreover, depending upon the epitopes mutated in a VEM, the VEM may not be detected by tests for HBsAg. "You could have someone with chronic hepatitis B and you wouldn't detect it," according to Dr. Levin.

Thus, even as the global hepatitis B immunization program continues to reduce new cases of hepatitis B infection and the enormous burden of chronic hepatitis B disease, it is simultaneously generating VEMs, thereby potentially sewing the seeds of the program's failure.

A second, entirely separate source of selection pressure promoting the creation of VEMs stems from the fact that lamivudine frequently leads to mutations in the gene for reverse transcriptase, which happens to overlap the surface antigen gene. These mutations can result in changes in the surface antigen protein, which under the wrong conditions will result in VEMs.

"The outcome will depend on whether the new mutant is stable, whether it can cause antigenic change in the neutralization characteristics of the surface antigen, whether it's transmissible from one person to another, and whether it can cause acute or chronic disease. But if all these things line up right, treatment with lamivudine could create a situation where you have more VEMs," Dr. Levin continued.

Lamivudine was the first nucleoside analog approved for the treatment of chronic hepatitis B infection. It remains widely used as monotherapy in many resource-poor countries because it is inexpensive, relatively free of side effects, and effective – at least initially. As has been seen with single-agent therapy in HIV and tuberculosis, however, lamivudine monotherapy eventually results in the appearance of lamivudine-resistant hepatitis B strains.

The World Health Organization is monitoring the hepatitis B VEM situation closely (Bull. World Health Org. 2010;88:66-73). One issue that's as yet unclear is whether emergence of VEMs will be accelerated by simultaneous use of the hepatitis B vaccine and treatment with lamivudine.

Dr. Levin disclosed that he has served as a consultant to Merck & Co. and GlaxoSmithKline. Both companies make hepatitis A and B vaccines. ■

Vaccine's Protection Against Hepatitis B: 20 Years and Up

BY BRUCE JANCIN

EXPERT ANALYSIS FROM A CONFERENCE ON PEDIATRIC INFECTIOUS DISEASES

VAIL, COLO. – Immunization at birth against hepatitis B protects against symptomatic disease for at least 20 years, despite frequent exposures, according to several recent studies.

Whether newborn immunization provides protection for life without the need for booster doses is still an open question.

Experts continue to monitor the hepatitis B vaccine's long-term effectiveness, and recommendations for booster doses will be issued, should evidence show they are necessary.

But the recent reports suggesting that the duration of protection is 2 decades and counting are quite encouraging, Dr. Myron J. Levin said at the conference, which was sponsored by the Children's Hospital, Denver.

He cited a meta-analysis by investigators at Tehran (Iran) University of Medical Sciences, who included 34 studies with more than 9,300 subjects.

The researchers determined that the rate of breakthrough infection was extremely low: 0% in the first 5 years post vaccination, 0.06% during years 6-10, 0.2% in years 11-15, and 0% in years 16-20 (Vaccine 2010;28:623-31).

It's absolutely necessary that physicians do a better job making sure neonates get a birth dose of vaccine while they're still in the hospital.

Even more encouraging was a study of 204 Thai children who were immunized at birth and born to chronically infected hepatitis B surface antigen–positive mothers.

These children, living in a highly endemic area for hepatitis B, have been followed for 17 years with annual clinic visits and serologic studies.

The frequent transient presence of hepatitis B surface antigen and/or hepatitis B core antibody indicated that these subjects were indeed heavily exposed to hepatitis B virus throughout their childhood and adolescence.

Yet no one with transient hepatitis B surface antigen developed any clinical symptoms of liver disease.

And no cases of chronic hepatitis B occurred in the study population (J. Infect. Dis. 2009;200:33-8). In other words, the vaccine did exactly what it's supposed to do: It prevented clinical disease, observed Dr. Levin, professor of pediatrics and medicine at the University of Colorado, Denver.

A key element in the persistence of protection against clinical hepatitis B in patients who were immunized as children is immune memory.

This was underscored in a study of 493 Alaskan children who had been immunized 22 years earlier, although not at birth. At follow-up, 60% of subjects still had protective levels of vaccine-induced antibody (defined as 10 mIU/mL).

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DR. LEVIN

Of the remaining 193 subjects, 160 (83%) demonstrated a rapid rise in antibody level in response to a booster. This early spike in antibody is evidence of immune memory, whereby the immune system is able to kick in and provide the needed protection upon exposure to hepatitis B, even though the level of protective antibody in a vaccinated person declines with time.

If it is assumed that immune memory indicates protection, 93% of subjects in this study were still protected against hepatitis B at 22 years after vaccination. The investigators concluded that booster doses aren't needed (J. Infect. Dis. 2009;200:1390-6).

Dr. Levin said that regardless of how long it ultimately turns out that protection against hepatitis B persists after childhood vaccination, it's absolutely necessary that physicians do a better job of making sure neonates get a birth dose of vaccine while they're still in the hospital. At present, this occurs in only about one-half of neonates born in the United States. As a result, roughly 8,000 infants per year are chronically infected with hepatitis B.

Dr. Levin disclosed that he has served as a consultant to Merck & Co. and GlaxoSmithKline. Both companies make hepatitis A and B vaccines. ■