

Hep B Vaccine Immunity May Wane After 15 Years

BY MIRIAM E. TUCKER

Senior Writer

BALTIMORE — Immunity to hepatitis B might wane 15 years after vaccination among those who received the vaccine series beginning at birth, Dr. Stephanie R. Bialek said at a conference on vaccine research sponsored by the National Foundation for Infectious Diseases.

Data from long-term follow-up studies have established that people who received

the three-dose hepatitis B vaccine series beginning after 6 months of age have long-term protection against chronic hepatitis B infection and do not need booster shots. In that population, breakthrough infections occur in only about 0%-7% of individuals more than 20 years after vaccination, and most of those are asymptomatic.

Chronic hepatitis B infection is extremely rare, occurring in fewer than 1%, said Dr. Bialek, a medical officer in the division of viral hepatitis at the Centers for Disease Control and Prevention.

However, it is not known whether the same is true for those who begin the vaccine series at birth, a practice that was first recommended in the United States in 1992.

Thus far, 10-year data in that population suggest that breakthrough infections are rare, occurring in 0%-6%, and there have been no reports of chronic infections among vaccine responders.

On the other hand, protective concentrations of antibody to hepatitis B surface antigen (anti-HBs), defined as levels greater than 10 mIU/mL, are present in fewer than 20% at 10 years, compared with more than 50% at 7-22 years among those vaccinated beginning after 6 months of age, Dr. Bialek noted.

Now, new data from an investigation conducted in Micronesia suggest that

protection in those vaccinated as newborns may begin to subside at around 15 years.

The Federated States of Micronesia, a U.S.-affiliated jurisdiction in the western Pacific where hepatitis B virus infection had historically been endemic, implemented hepatitis B vaccination beginning at birth in 1989.

Micronesian adolescents who had received three doses of recombinant hepatitis B vaccine (at birth, 2 months, and 6 months of age) and who had tested negative for antibody to hepatitis B core antigen (anti-HBc) 2 years after the primary vaccination were followed for 15 years after the primary vaccination. Recombivax had been given in doses of 5 mcg at birth, followed by doses of 2.5 mcg at 2 and 6 months. Today, 5 mcg is recommended for all three doses, she noted.

In 2006, investigators were able to track down 105 of the 238 children who had received three doses of hepatitis B vaccine, were anti-HBc-negative, and had been tested for anti-HBs at 35 months. By then, they had a median age of 15.8 years, with a median of 15.1 years since completion of the vaccine series. A total of eight

(7.6%) were anti-HBc-positive, but none was HBsAg-positive.

Booster doses of vaccine were given to the 96 who were anti-HBc-negative in 2006. Of these, only 7 (7%) had anti-HBs concentrations greater than 10 mIU/mL

at the time they were given the booster, and only about half (45, or 47%) had anamnestic anti-HBs responses at 14 days after the booster (defined as an increase in anti-HBs concentration greater than 10 mIU/mL). Absence of an anamnestic response might indicate waning immunity,

Dr. Bialek said at the meeting.

Limitations of this study include the fact that maternal HBsAg status was not known, postvaccination testing had not been performed (some of the participants may have been nonresponders), and the vaccine dose used for the second and third doses was half of the currently recommended dose. And importantly, "Just because they didn't boost doesn't mean they're not protected," Dr. Bialek said in an interview following her presentation. At least two ongoing studies are investigating this issue further, she added. ■

LEXAPRO® (escitalopram oxalate) TABLETS/ORAL SOLUTION

(3% and <1%); Anorgasmia* (2% and <1%). *Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo B Lexapro: headache, upper respiratory tract infection, back pain, pharyngitis, inflamed injury, anxiety. †Primarily ejaculatory delay. ‡Denominator used was for males only (N=225 Lexapro; N=188 placebo). †Denominator used was for females only (N=490 Lexapro; N=404 placebo). **Generalized Anxiety Disorder Table 3** enumerates the incidence, rounded to the nearest percent of treatment-emergent adverse events that occurred among 429 GAD patients who received Lexapro 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients. The most commonly observed adverse events in Lexapro patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were nausea, ejaculation disorder (primarily ejaculatory delay), insomnia, fatigue, decreased libido, and anorgasmia (see TABLE 3). **TABLE 3. Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Generalized Anxiety Disorder* (Lexapro (N=429) and Placebo (N=427)).** **Autonomic Nervous System Disorders:** Dry Mouth (9% and 5%); Sweating Increased (4% and 1%). **Central & Peripheral Nervous System Disorders:** Headache (24% and 17%); Paresthesia (2% and 1%); Indigestion (3% and 2%); Vomiting (3% and 1%); Abdominal Pain (2% and 1%); Flatulence (2% and 1%); Toothache (2% and 0%). **General:** Fatigue (9% and 2%); Influenza-like symptoms (5% and 4%); **Musculoskeletal:** Neck/Shoulder Pain (3% and 1%). **Psychiatric Disorders:** Somnolence (13% and 7%); Insomnia (12% and 6%); Libido Decreased (7% and 2%); Dreaming Abnormal (3% and 2%); Appetite Decreased (3% and 1%); Lethargy (3% and 1%); Yawning (2% and 1%); **Urogenital:** Ejaculation Disorder[†] (14% and 2%); Anorgasmia* (6% and <1%); Menstrual Disorder (2% and 1%). *Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo B Lexapro: inflamed injury, dizziness, back pain, upper respiratory tract infection, rhinitis, pharyngitis. †Primarily ejaculatory delay. ‡Denominator used was for males only (N=182 Lexapro; N=195 placebo). †Denominator used was for females only (N=247 Lexapro; N=232 placebo). **Dose Dependency of Adverse Events** The potential dose dependency of common adverse events (defined as an incidence rate of 15% in either the 10 mg or 20 mg Lexapro groups) was examined on the basis of the combined incidence of adverse events in two fixed-dose trials. The overall incidence rates of adverse events in 10 mg Lexapro-treated patients (66%) was similar to that of the placebo-treated patients (61%), while the incidence rate in 20 mg/day Lexapro-treated patients was greater (86%). **Table 4** shows common adverse events that occurred in the 20 mg/day Lexapro group with an incidence that was approximately twice that of the 10 mg/day Lexapro group and approximately twice that of the placebo group. **TABLE 4. Incidence of Common Adverse Events* in Patients with Major Depressive Disorder Receiving Placebo (N=311), 10 mg/day Lexapro (N=310), 20 mg/day Lexapro (N=125).** **Insomnia** (4%, 7%, 14%); **Diarrhea** (5%, 6%, 14%); **Dry Mouth** (3%, 4%, 9%); **Somnolence** (1%, 4%, 9%); **Dizziness** (2%, 4%, 7%); **Sweating Increased** (<1%, 3%, 8%); **Constipation** (1%, 3%, 6%); **Fatigue** (2%, 2%, 6%); **Indigestion** (1%, 2%, 6%). *Adverse events with an incidence rate of at least 5% in either of the Lexapro groups and with an incidence rate in the 20 mg/day Lexapro group that was approximately twice that of the 10 mg/day Lexapro group and the placebo group. **Male and Female Sexual Dysfunction with SSRIs** Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence. **Table 5** shows the incidence rates of sexual side effects in patients with major depressive disorder and GAD in placebo-controlled trials. **TABLE 5. Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials (In Males Only: Lexapro (N=107) and Placebo (N=303)); Ejaculation Disorder (primarily ejaculatory delay) (12% and 1%); Libido Decreased (6% and 2%); Impotence (2% and <1%). (In Females Only: Lexapro (N=137) and Placebo (N=636)):** Libido Decreased (3% and 1%); Anorgasmia* (3% and <1%) There are no adequately designed studies examining sexual dysfunction with escitalopram treatment. Pragmatism has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects. **Vital Sign Changes** Lexapro and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with Lexapro treatment. In addition, a comparison of supine and standing vital sign measures in subjects receiving Lexapro indicated that Lexapro treatment is not associated with orthostatic changes. **Weight Changes** Patients treated with Lexapro in controlled trials did not differ from placebo-treated patients with regard to clinically important change in body weight. **Laboratory Changes** Lexapro and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables, and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Lexapro treatment. **ECG Changes** Electrocardiograms from Lexapro (N=625), racemic citalopram (N=351), and placebo (N=527) groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed (1) a decrease in heart rate of 2.2 bpm for Lexapro and 2.7 bpm for racemic citalopram, compared to an increase of 0.3 bpm for placebo and (2) an increase in QTc interval of 3.9 msec for Lexapro and 3.7 msec for racemic citalopram, compared to 0.5 msec for placebo. Neither Lexapro nor racemic citalopram were associated with the development of clinically significant ECG abnormalities. **Other Events Observed During the Premarketing Evaluation of Lexapro** Following is a list of WHO terms that reflect treatment-emergent adverse events, as defined in the introduction to the **ADVERSE REACTIONS** section, reported by the 1428 patients treated with Lexapro for periods of up to one year in double-blind or open-label clinical trials during its premarketing evaluation. All reported events are included except those already listed in **Tables 2 & 3**, those occurring in only one patient, event terms that are so general as to be uninformative, and those that are unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with Lexapro, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients. **Cardiovascular -** Frequent: palpitation, hypertension. **Infrequent:** bradycardia, tachycardia, ECG abnormal, flushing, varicose vein. **Central and Peripheral Nervous System Disorders -** Frequent: light-headed feeling, migraine. **Infrequent:** tremor, vertigo, restless legs, shakiness, twitching, dysequilibrium, tics, carpal tunnel syndrome, muscle contractions involuntary, sluggishness, coordination abnormal, faintness, hyperreflexia, muscular tone increased. **Gastrointestinal Disorders -** Frequent: heartburn, abdominal cramp, gastroenteritis. **Infrequent:** gastroesophageal reflux, bloating, abdominal discomfort, dyspepsia, increased stool frequency, belching, gastritis, hemorrhoids, gagging, polyposis gastric, swallowing difficult. **General -** Frequent: allergy, pain in limb, fever, hot flushes, chest pain. **Infrequent:** edema of extremities, chills, lightness of chest, leg pain, asthenia, syncope, malaise, anaphylaxis, fall. **Hemic and Lymphatic Disorders -** Infrequent: bruise, anemia, nosebleed, hematoma, lymphadenopathy cervical. **Metabolic and Nutritional Disorders -** Frequent: increased weight. **Infrequent:** decreased weight, hyperglycemia, thirst, bilirubin increased, hepatic enzymes increased, gout, hypercholesterolemia. **Musculoskeletal System Disorders -** Frequent: arthralgia, myalgia. **Infrequent:** jaw stiffness, muscle cramp, muscle stiffness, arthritis, muscle weakness, back discomfort, arthropathy, jaw pain, joint stiffness. **Psychiatric Disorders -** Frequent: appetite increased, lethargy, irritability, concentration impaired. **Infrequent:** jitteriness, panic reaction, agitation, apathy, forgetfulness, depression aggravated, nervousness, restlessness aggravated, suicide attempt, amnesia, anxiety attack, bruising, carbohydrate craving, confusion, depersonalization, disorientation, emotional lability, feeling unreal, tremulousness nervous, crying abnormal, depression, excitability, auditory hallucination, suicidal tendency. **Reproductive Disorders/Female -** Frequent: menstrual cramps, menstrual disorder. **Infrequent:** menorrhagia, breast neoplasm, pelvic inflammation, premenstrual syndrome, spotting between menses. *% based on female subjects only. **N= 905 Respiratory System Disorders -** Frequent: bronchitis, sinus congestion, coughing, nasal congestion, sinus headache. **Infrequent:** asthma, breath shortness, laryngitis, pneumonia, tracheitis. **Skin and Appendages Disorders -** Frequent: rash. **Infrequent:** pruritus, acne, alopecia, eczema, dermatitis, dry skin, folliculitis, lipoma, furunculosis, dry lips, skin nodule. **Special Senses -** Frequent: vision blurred, tinnitus. **Infrequent:** taste alteration, earache, conjunctivitis, vision abnormal, dry eyes, eye irritation, visual disturbance, eye infection, pupils dilated, metallic taste. **Urinary System Disorders -** Frequent: urinary frequency, urinary tract infection. **Infrequent:** urinary urgency, kidney stone, dysuria, blood in urine. **Events Reported Subsequent to the Marketing of Escitalopram** Although no causal relationship to escitalopram treatment has been found, the following adverse events have been reported to have occurred in patients and to be temporally associated with escitalopram treatment during post marketing experience and were not observed during the premarketing evaluation of escitalopram: abnormal gait, acute renal failure, aggression, akathisia, allergic reaction, angioedema, atrial fibrillation, choreoathetosis, delirium, delusion, diplopia, dysarthria, dyskinesia, dystonia, ecchymosis, erythema multiforme, extrapyramidal disorders, fulminant hepatitis, hepatic failure, hypoaesthesia, hypoglycemia, hypokalemia, INR increased, gastrointestinal hemorrhage, glaucoma, grand mal seizures (or convulsions), hemolytic anemia, hepatic necrosis, hepatitis, hypotension, leucopenia, myocardial infarction, myoclonus, neuroleptic malignant syndrome, nightmares, nystagmus, orthostatic hypotension, pancreatitis, paranoia, photosensitivity reaction, priapism, prolactinemia, prothrombin decreased, pulmonary embolism, QT prolongation, rhabdomyolysis, seizures, serotonin syndrome, SIADH, spontaneous abortion, Stevens Johnson Syndrome, tardive dyskinesia, thrombocytopenia, thrombosis, torsades de pointes, toxic epidermal necrolysis, ventricular arrhythmia, ventricular tachycardia and visual hallucinations.

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Analysis Refutes Hepatitis B Vaccine, RA Link

BY MIRIAM E. TUCKER

Senior Writer

BALTIMORE — The hepatitis B vaccine does not appear to be associated with an increased risk for rheumatoid arthritis, Dr. Roger P. Baxter and his associates reported at a vaccine research conference sponsored by the National Foundation for Infectious Diseases.

Both acute and chronic arthropathies have been reported in adults vaccinated with the tetanus-diphtheria (Td), hepatitis B (HepB), and measles-mumps-rubella (MMR) vaccines. However, most of the evidence to support or refute a causal relationship between the Td or HepB vaccine and chronic arthritis has come from isolated case reports, uncontrolled observational studies, or studies that lacked sufficient statistical power, said Dr. Baxter, associate director of the Vaccine Study Center at Kaiser Permanente, Oakland, Calif., and his associates.

A case-control analysis designed to overcome the shortcomings of the previous studies included a cohort of continuous enrollees in Northern California Kaiser Permanente's health plan from Jan. 1, 1995, through Dec. 31, 1999, who were aged 15-59 years during Jan. 1,

1997-Dec. 31, 1999. Individuals who had made clinic visits for rheumatoid arthritis (RA) and other inflammatory conditions prior to their follow-up start date were excluded.

A total of 416 incident cases of RA were identified (based on definitive diagnosis at the time or subsequent assessment by a rheumatologist), and each was matched with three controls based on age and the number of clinic visits made during the year prior to the onset date. Rates of hepatitis B vaccination among the RA patients were compared with those of controls, with adjustment for sex, age, and exact number of clinic visits. Similar comparisons were made for the tetanus and influenza vaccines.

No statistically significant risk of RA was found for any of the three vaccines. Only 1% of RA patients versus 0.6% of controls had been exposed to the hepatitis B vaccine within 1-90 days of onset of RA symptoms, for an adjusted odds ratio of 1.48.

Within 1-180 days, the percentages were 1.9% with RA versus 0.9% of controls, giving a still insignificant odds ratio of 2.01. Within 1 year, 2.4% of RA cases and 1.6% of controls had been exposed to the vaccine, again insignificant at 1.42.

In all, only 10 of the 416 RA patients had

received the HepB vaccine within 1 year of symptom onset, suggesting that "If there is an association, these data would imply that hepatitis B vaccine would only contribute to a small minority of cases," Dr. Baxter and his associates said in their poster.

Results for the other two vaccines were also not significant, with adjusted odds ratios of 0.77-1.06 for tetanus and 0.66-1.11 for influenza.

Health care utilization was higher among those with RA, which was a slight confounder in this study despite the attempt to control for number of visits: Even after adjustment, there was still a significant residual effect for number of visits, with an odds ratio of 1.15.

"Basically, people who get vaccines of all kinds are different from those who don't, and underlying differences may confound the relationship with things like RA. We try to control for these factors by matching and analyses, but still we think there are differences. ... People who have RA are more likely to be higher utilizers and also more likely to have gotten vaccines than people who don't utilize the system as much," Dr. Baxter said in a follow-up interview.

However, he added, although the difference in utilization was statistically significant, it probably wasn't that different clinically. "We thought initially this was an important confounder. But in the end we found that although they were different, in reality we could adjust for the vast majority of the difference." ■



'People who have RA are more likely to be higher utilizers and also more likely to have gotten vaccines.'

DR. BAXTER