# Adding Immunoglobulin to HBV Vaccine No Help

VITALS

**Major Finding:** The addition of hepatitis B immunoglobulin to hepatitis B prophylaxis with the recombinant HBV vaccine does not confer additional protection to newborns of chronically infected mothers.

**Data Source:** A randomized controlled trial of 222 infants born to mothers who tested positive for hepatitis B surface antigen.

**Disclosures:** Dr. Sarin and Dr. Pande reported having no relevant financial disclosures.

BY DIANA MAHONEY

FROM THE ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

BOSTON – The recombinant hepatitis B vaccine confers as much protection when given alone as it does when given together with hepatitis B immunoglobulin to newborns of chronically infected mothers, but neither regimen is optimally effective, a study has shown.

The randomized controlled trial assessed the hepatitis B virus (HBV) status of 222 infants born to mothers who tested positive for hepatitis B surface antigen (HBsAg). The rate of protection observed in infants who received only the vaccine was statistically similar to that of infants who received the vaccine plus hepatitis B immune globulin (HBIG).

A total of 39% of the vaccine-only group and 41% of the combination group remained infection free at a minimum of 18 weeks after birth, Dr. Shiv K. Sarin reported at the meeting, noting that nearly half of the babies in both groups developed occult HBV infections.

The current standard of care for preventing HBV infection in babies born to mothers who are HBsAg positive is the recombinant hepatitis B virus vaccine plus HBIG; however, previous studies have suggested the possibility that the vaccine alone may be as effective as the combination therapy, said Dr. Sarin of the Institute of Liver and Biliary Sciences in New Delhi.

To test this hypothesis, Dr. Sarin, along with lead investigator Dr. Chandana Pande, a research associate at G.B. Pant Hospital in New Delhi, and colleagues randomized the newborns of 222 women who screened positive for HBsAg during their prenatal care to receive the 0.5-mL recombinant HBV vaccine at birth, 6 weeks, 10 weeks, and 14 weeks, either alone (116 infants) or with 0.5 mL intramuscular HBIG (106 infants). Mothers on antiviral therapy and those with coinfections were excluded from the investigation, he said.

All of the babies were assessed at a minimum of 18 weeks for HBsAg, HBV-DNA, and antibodies to HBsAg (anti-HBs). The study's primary end point was freedom from overt or occult HBV infection with adequate immune response, defined as anti-HBs titers of at least 10 IU/mL, Dr. Sarin said in a poster presentation.

Babies with overt HBV infection were those whose blood specimens tested positive for HBsAg by enzyme-linked immunosorbent assay, whereas babies with occult infection were negative for HBsAg but positive for HBV-DNA by polymerase chain reaction testing, he said. Babies with no infection but whose anti-HBs titers were less than 10 IU/mL were categorized as having a poor immune response.

At 18 weeks after birth, there were no significant differences between the combination therapy group and monotherapy group with respect to the number of babies meeting the study's primary end point, Dr. Sarin reported. Specifically, 43 babies in the combination group and 45 in the vaccine-only group remained free of overt or occult HBV infection with adequate immune response.

Of the babies not meeting the primary end point, 9 had overt HBV infection, including 2 in the combination group and 7 in the vaccine-only group, and 106 developed occult HBV infection, including 52 in the combination group and 54 in the vaccine-only group, Dr. Sarin said. Neither of these differences attained statistical significance, nor did the between-group difference in the number of infants demonstrating a poor immune response, he said. ■

**Brief Summary** (For full Prescribing Information refer to package insert.)

**INDICATIONS AND USAGE**
OFIRMEV™ (acetaminophen) injection is indicated for
- the management of mild to moderate pain
- the management of moderate to severe pain with adjunctive opioid analgesics
- the reduction of fever.

**CONTRAINDICATIONS**
Acetaminophen is contraindicated:
- in patients with known hypersensitivity to acetaminophen or to any of the excipients in the intravenous formulation.
- in patients with severe hepatic impairment or severe active liver disease.

**WARNINGS AND PRECAUTIONS**
**Hepatic Injury**
Administration of acetaminophen in doses higher than recommended may result in hepatic injury, including the risk of severe hepatotoxicity and death. Do not exceed the maximum recommended daily dose of acetaminophen.

Use caution when administering acetaminophen in patients with the following conditions: hepatic impairment or active hepatic disease, alcoholism, chronic malnutrition, severe hypovolemia (e.g., due to dehydration or blood loss), or severe renal impairment (creatinine clearance ≤ 30 mL/min).

**Allergy and Hypersensitivity**
There have been post-marketing reports of hypersensitivity and anaphylaxis associated with the use of acetaminophen. Clinical signs included swelling of the face, mouth, and throat, respiratory distress, urticaria, rash, and pruritus. There were infrequent reports of life-threatening anaphylaxis requiring emergent medical attention. Discontinue OFIRMEV immediately if symptoms associated with allergy or hypersensitivity occur. Do not use OFIRMEV in patients with acetaminophen allergy.

**ADVERSE REACTIONS**
The following serious adverse reactions are discussed elsewhere in the labeling:
- Hepatic Injury
- Allergy and Hypersensitivity

**Clinical Trial Experience**
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in practice.

**Adult Population**
A total of 1020 adult patients have received OFIRMEV in clinical trials, including 37.3% (n=380) who received 5 or more doses, and 17.0% (n=173) who received more than 10 doses. Most patients were treated with OFIRMEV 1000 mg every 6 hours. A total of 13.1% (n=134) received OFIRMEV 650 mg every 4 hours.

All adverse reactions that occurred in adult patients treated with either OFIRMEV or placebo in repeated dose, placebo-controlled clinical trials at an incidence ≥ 3% and at a greater frequency than placebo are listed in Table 1. The most common adverse events in adult patients treated with OFIRMEV (incidence ≥ 5% and greater than placebo) were nausea, vomiting, headache, and insomnia.

**Table 1. Treatment-Emergent Adverse Reactions Occurring ≥ 3% in OFIRMEV and at a greater frequency than Placebo in Placebo-Controlled, Repeated Dose Studies**

| System Organ Class – Preferred Term | OFIRMEV (N=402) n (%) | PLACEBO (N=379) n (%) |
|---|---|---|
| **Gastrointestinal Disorders** | | |
| Nausea | 138 (34) | 119 (31) |
| Vomiting | 62 (15) | 42 (11) |
| **General Disorders and Administration Site Conditions** | | |
| Pyrexia* | 22 (5) | 52 (14) |
| **Nervous System Disorders** | | |
| Headache | 39 (10) | 33 (9) |
| **Psychiatric Disorders** | | |
| Insomnia | 30 (7) | 21 (5) |

* Pyrexia adverse reaction frequency data is included in order to alert healthcare practitioners that the antipyretic effects of OFIRMEV may mask fever.

Other Adverse Reactions Observed During Clinical Studies of OFIRMEV in Adults

The following additional treatment-emergent adverse reactions were reported by adult subjects treated with OFIRMEV in all clinical trials (n=1020) that occurred with an incidence of at least 1% and at a frequency greater than placebo (n=525).

Blood and lymphatic system disorders: anemia
General disorders and administration site conditions: fatigue, infusion site pain, edema peripheral
Investigations: aspartate aminotransferase increased, breath sounds abnormal
Metabolism and nutrition disorders: hypokalemia
Musculoskeletal and connective tissue disorders: muscle spasms, trismus
Psychiatric disorders: anxiety
Respiratory, thoracic and mediastinal disorders: dyspnea
Vascular disorders: hypertension, hypotension

**Pediatric population**
A total of 355 pediatric patients (47 neonates, 64 infants, 171 children, and 73 adolescents) have received OFIRMEV in active-controlled (n=250) and open-label clinical trials (n=225), including 59.7% (n=212) who received 5 or more doses and 43.1% (n=153) who received more than 10 doses. Pediatric patients received OFIRMEV doses up to 15 mg/kg on an every 4 hours, every 6 hours, or every 8 hours schedule. The maximum exposure was 7.7, 6.4, 6.8, and 7.1 days in neonates, infants, children, and adolescents, respectively.

The most common adverse events (incidence ≥ 5%) in pediatric patients treated with OFIRMEV were nausea, vomiting, constipation, pruritus, agitation, and atelectasis.

Other Adverse Reactions Observed During Clinical Studies of OFIRMEV in Pediatrics

The following additional treatment-emergent adverse reactions were reported by pediatric subjects treated with OFIRMEV (n=355) that occurred with an incidence of at least 1%.

Blood and lymphatic system disorders: anemia
Cardiac disorders: tachycardia
Gastrointestinal disorders: abdominal pain, diarrhea
General disorders and administration site conditions: injection site pain, edema peripheral, pyrexia
Investigations: hepatic enzyme increase
Metabolism and nutrition disorders: hypoalbuminemia, hypokalemia, hypomagnesemia, hypophosphatemia, hypervolemia
Musculoskeletal and connective tissue disorders: muscle spasm, pain in extremity
Nervous system disorders: headache
Psychiatric disorders: insomnia
Renal and urinary disorders: oliguria
Respiratory, thoracic and mediastinal disorders: pulmonary edema, hypoxia, pleural effusion, stridor, wheezing
Skin and subcutaneous tissue disorders: periorbital edema, rash
Vascular disorders: hypertension, hypotension

**DRUG INTERACTIONS**
**Effects of other Substances on Acetaminophen**
Substances that induce or regulate hepatic cytochrome enzyme CYP2E1 may alter the metabolism of acetaminophen and increase its hepatotoxic potential. The clinical consequences of these effects have not been established. Effects of ethanol are complex, because excessive alcohol usage can induce hepatic cytochromes, but ethanol also acts as a competitive inhibitor of the metabolism of acetaminophen.

**Anticoagulants**
Chronic oral acetaminophen use at a dose of 4000 mg/day has been shown to cause an increase in international normalized ratio (INR) in some patients who have been stabilized on sodium warfarin as an anticoagulant. As no studies have been performed evaluating the short-term use of OFIRMEV in patients on oral anticoagulants, more frequent assessment of INR may be appropriate in such circumstances.

**USE IN SPECIFIC POPULATIONS**
**Pregnancy**
Pregnancy Category C. There are no studies of intravenous acetaminophen in pregnant women; however, epidemiological data on oral acetaminophen use in pregnant women show no increased risk of major congenital malformations. Animal reproduction studies have not been conducted with IV acetaminophen, and it is not known whether OFIRMEV can cause fetal harm when administered to a pregnant woman. OFIRMEV should be given to a pregnant woman only if clearly needed.

The results from a large population-based prospective cohort, including data from 26,424 women with live born singletons who were exposed to oral acetaminophen during the first trimester, indicate no increased risk for congenital malformations, compared to a control group of unexposed children. The rate of congenital malformations (4.3%) was similar to the rate in the general population. A population-based, case-control study from the National Birth Defects Prevention Study showed that 11,610 children with prenatal exposure to acetaminophen during the first trimester had no increased risk of major birth defects compared to 4,500 children in the control group. Other epidemiological data showed similar results.

While animal reproduction studies have not been conducted with intravenous acetaminophen, studies in pregnant rats that received oral acetaminophen during organogenesis at doses up to 0.85 times the maximum human daily dose (MHDD = 4 grams/day, based on a body surface area comparison) showed evidence of fetotoxicity (reduced fetal weight and length) and a dose-related increase in bone variations (reduced ossification and rudimentary rib changes). Offspring had no evidence of external, visceral, or skeletal malformations. When pregnant rats received oral acetaminophen throughout gestation at doses of 1.2-times the MHDD (based on a body surface area comparison), areas of necrosis occurred in both the liver and kidney of pregnant rats and fetuses.

In a continuous breeding study, pregnant mice received 0.25, 0.5, or 1.0% acetaminophen via the diet (357, 715, or 1430 mg/kg/day). These doses are approximately 0.43, 0.87, and 1.7 times the MHDD, respectively, based on a body surface area comparison. A dose-related reduction in body weights of fourth and fifth litter offspring of the treated mating pair occurred during lactation and post-weaning at all doses. Animals in the high dose group had a reduced number of litters per mating pair, male offspring with an increased percentage of abnormal sperm, and reduced birth weights in the next generation pups.

**Labor and Delivery**
There are no adequate and well-controlled studies with OFIRMEV during labor and delivery; therefore, it should be used in such settings only after a careful benefit-risk assessment.

**Nursing Mothers**
While studies with OFIRMEV have not been conducted, acetaminophen is secreted in human milk in small quantities after oral administration. Based on data from more than 15 nursing mothers, the calculated infant daily dose of acetaminophen is approximately 1 – 2% of the maternal dose. There is one well-documented report of a rash in a breast-fed infant that resolved when the mother stopped acetaminophen use and recurred when she resumed acetaminophen use. Caution should be exercised when OFIRMEV is administered to a nursing woman.

**Pediatric Use**
The safety and effectiveness of OFIRMEV for the treatment of acute pain and fever in pediatric patients ages 2 years and older is supported by evidence from adequate and well-controlled studies of OFIRMEV in adults. Additional safety and pharmacokinetic data were collected in 355 patients across the full pediatric age strata, from premature neonates (≥ 32 weeks post menstrual age) to adolescents. The effectiveness of OFIRMEV for the treatment of acute pain and fever has not been studied in pediatric patients < 2 years of age.

**Geriatric Use**
Of the total number of subjects in clinical studies of OFIRMEV, 15% were age 65 and over, while 5% were age 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

**Patients with Hepatic Impairment**
Acetaminophen is contraindicated in patients with severe hepatic impairment or severe active liver disease and should be used with caution in patients with hepatic impairment or active liver disease. A reduced total daily dose of acetaminophen may be warranted.

**Patients with Renal Impairment**
In cases of severe renal impairment (creatinine clearance ≤ 30 mL/min), longer dosing intervals and a reduced total daily dose of acetaminophen may be warranted.

**OVERDOSAGE**
**Signs and Symptoms**
In acute acetaminophen overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia may also occur. Plasma acetaminophen levels > 300 mcg/mL at 4 hours after oral ingestion were associated with hepatic damage in 90% of patients; minimal hepatic damage is anticipated if plasma levels at 4 hours are < 150 mcg/mL or < 37.5 mcg/mL at 12 hours after ingestion. Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis, and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

**PHARMACOKINETICS**
The pharmacokinetics of OFIRMEV have been studied in patients and healthy subjects from premature neonates up to adults 60 years old. The pharmacokinetic profile of OFIRMEV has been demonstrated to be dose proportional in adults following administration of single doses of 500, 650, and 1000 mg.

The maximum concentration ($C_{max}$) occurs at the end of the 15 minute intravenous infusion of OFIRMEV. Compared to the same dose of oral acetaminophen, the $C_{max}$ following administration of OFIRMEV is up to 70% higher, while overall exposure (area under the concentration time curve [AUC]) is very similar.

The pharmacokinetic exposure of OFIRMEV observed in children and adolescents is similar to adults, but higher in neonates and infants. Dosing simulations from pharmacokinetic data in infants and neonates suggest that dose reductions of 33% in infants 1 month to < 2 years of age, and 50% in neonates up to 28 days, with a minimum dosing interval of 6 hours, will produce a pharmacokinetic exposure similar to that observed in children age 2 years and older.

**NONCLINICAL TOXICOLOGY**
**Carcinogenesis**
Long-term studies in mice and rats have been completed by the National Toxicology Program to evaluate the carcinogenic potential of acetaminophen. In 2-year feeding studies, F344/N rats and B6C3F1 mice were fed a diet containing acetaminophen up to 6000 ppm. Female rats demonstrated equivocal evidence of carcinogenic activity based on increased incidences of mononuclear cell leukemia at 0.8 times the maximum human daily dose (MHDD) of 4 grams/day, based on a body surface area comparison. In contrast, there was no evidence of carcinogenic activity in male rats (0.7 times) or mice (1.2-1.4 times the MHDD, based on a body surface area comparison).

**Mutagenesis**
Acetaminophen was not mutagenic in the bacterial reverse mutation assay (Ames test). In contrast, acetaminophen tested positive in the in vitro mouse lymphoma assay and the in vitro chromosomal aberration assay using human lymphocytes. In the published literature, acetaminophen has been reported to be clastogenic when administered a dose of 1500 mg/kg/day to the rat model (3.6-times the MHDD, based on a body surface area comparison). In contrast, no clastogenicity was noted at a dose of 750 mg/kg/day (1.8-times the MHDD, based on a body surface area comparison), suggesting a threshold effect.

**Impairment of fertility**
In studies conducted by the National Toxicology Program, fertility assessments have been completed in Swiss mice via a continuous breeding study. There were no effects on fertility parameters in mice consuming up to 1.7 times the MHDD of acetaminophen, based on a body surface area comparison. Although there was no effect on sperm motility or sperm density in the epididymis, there was a significant increase in the percentage of abnormal sperm in mice consuming 1.7 times the MHDD (based on a body surface area comparison) and there was a reduction in the number of mating pairs producing a fifth litter at this dose, suggesting the potential for cumulative toxicity with chronic administration of acetaminophen near the upper limit of daily dosing.

Published studies in rodents report that oral acetaminophen treatment of male animals at doses that are 1.2 times the MHDD and greater (based on a body surface area comparison) result in decreased testicular weights, reduced spermatogenesis, reduced fertility, and reduced implantation sites in females given the same doses. These effects appear to increase with the duration of treatment. The clinical significance of these findings is not known.

OFIRMEV (acetaminophen) injection

Manufactured for:
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OFIRMEV (acetaminophen) injection

Revised 11/2010

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U.S. PATENT NUMBERS: 6,028,222; 6,992,218

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