Study Title: Comparison the seroconversion rate between two-dose and three-dose regimens of Heplisav B among patients with cirrhosis, a randomized-control prospective study.
Sponsor: Self-sponsored

Indication: Patient outcomes

Medical Director:
Paul Thuluvath, MD, FRCP
Tele: (410)-332-9308
Fax: (410)-659-2917

Principal Investigator: Paul Thuluvath, MD

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Primary Objective: The rates of seroconversion (defined as an HBsAg antibody concentration ≥ 10 mIU/ml) after two doses of Heplisav-B given at 0 and 4 weeks versus three doses of Heplisav-B given at 0, 4 weeks, and 8 weeks.

Secondary Objective: Factors are associated with a lower likelihood of achieving immunogenicity, such as age, race, MELD scores, etiologies of cirrhosis (NAFLD, HCV, ALD, AIH, PBC, PSC, others), comorbidities (chronic obstructive pulmonary disease, diabetes mellitus, hypertension, coronary artery disease, renal failure, obesity), immunosuppression.
*MELD: Model for End Stage Liver Disease, NAFLD: Nonalcoholic Fatty Liver Disease, HCV: Hepatitis C, ALD: Alcohol induced Liver Disease, AIH: Autoimmune Hepatitis, PBC: Primary Biliary Cholangitis, PSC: Primary Sclerosing Cholangitis.
1. Study Rationale:

Hepatitis B virus is a major cause of acute and chronic liver disease both in the United States and worldwide. In 2016, an estimated 862,000 people were living with HBV infection in the US with a total of 1,649 U.S. death certificates recorded as an underlying or contributing cause of death (1). Chronic infection may cause liver cirrhosis and hepatocellular carcinoma (HCC). Since the introduction of the vaccine in the 1990s, there has been a significant decline in the incidence of HBV infection. Approved in November 2017, Heplisav-B uses a synthetic cytosine phosphoguanine oligonucleotide derived from bacterial DNA; it is thought to stimulate the immune system through activation of the toll-like receptor 9 pathway, which induces production of cytokines such as interleukines such as interleukine-12 and interferon-alpha (2). It has been shown to induce higher immunity in healthy individuals compared to the conventional vaccines. The vaccine titer should be checked 8 to 12 weeks after administration of the vaccination series. Good responders were defined as those having the anti-HBs titer were ≥ 100 mUI/ml, poor responders having anti-HBs titer between 10 and 99 mUI/ml, and nonresponders having anti-HBs titer < 10 mIU/ml (3) Seroprotection rate by age group in healthy population is 100% in 18-29 year old group, 98.9% in 30-29% year old group, 97.2% in 40-49 year old group, 95.2% in 50-59 year old group,

91.6% in 60-70 year old group (4). However, 5% of the general population will not mount a protection response. Response to HBV vaccine is variable among patients with chronic diseases, such as HIV infection, celiac disease, IBD, end stage renal disease, diabetes. Immunogenicity of hepatitis B vaccine is also lower in decompensated cirrhosis (5), (6). Among cirrhotic patients, only 45% who received Heplisav-B achieved immunity (7). The best approach to HBV vaccine nonresponse is repeating the vaccine series at the same dose and using the same route in noninfected individuals (4).

2. Investigational Plan

*Study Design & Duration: All the cirrhosis patients presented to our hepatology clinic in Mercy Medical Center between 09/2020 and 07/2021 who do not have immunity against Hepatitis B (defined as anti-HBs titer < 10 mIU/ml) will be recruited. Patients will be stratified based on vaccine naive and vaccine experienced. Patients who had more than one vaccination series will not be included. Previous vaccination could be either Heplisav or Engerix; however, this information will be collected.

We will perform a randomized control study prospectively into two groups, those who receive Heplisav-B in 0, 4 weeks and those who receive Heplisav-B in 0, 4, 8 weeks. The vaccine titer should be checked 8 to 12 weeks after administration of the vaccination series and classified into good responders, poor responders, and nonresponders based on antibody titers.

We will collect their basic data including age, MELD scores, etiologies of cirrhosis (NAFLD, HCV, ALD, AIH, PBC, PSC, others), comorbidities (chronic obstructive pulmonary disease, diabetes mellitus, hypertension, coronary artery disease, renal failure, obesity), previous HBV vaccine, immunosuppression.

Primary endpoint: Seroconversion or immunity is defined as HBsAb level ≥ 10 mIU/ml.

Randomization process:
We will use the envelope allocation technique. At first, we will create a sequentially numbered random group assignment. The supplies for the randomization envelopes include envelopes, back carbon paper, and white copy paper. On the white copy paper, we will write the study ID. We will wrap the white copy paper inside the black carbon paper, put those into the envelope and seal it. Then we will attach the envelope to the consent form and give it to the patient.

The above data will be prospectively collected and entered into an excel database in a de-identified mode by giving them a coded number. We will save data in a password-protected format and filed in the GI Research share drive and only the study staff will have access to the file to download for any study procedure or audit. It will be stored in a confidential manner, indefinite in a secured Mercy share drive according to the 21 CFR part 11 guidelines.

Sample size for both arms: 200. Current seroconversion rate of hepatitis B vaccine in cirrhosis is low, about 50%, with the conventional schedule, either Engerix 0, 1 month, 6 months or Heplisav-B 0, 1

month. We aim for the seroconversion rate of 70% with Heplisav-B 0, 1 month, 2 months. The probability of type I error is 5% and the power is 80%.

3. Inclusion criteria

- All the cirrhosis patients more than 18 years old presented to our hepatology clinic in Mercy Medical Center between 09/2020 and 07/2021 who do not have immunity against Hepatitis B (defined as anti-HBs titer < 10 mIU/ml) will be recruited.

4. Exclusion criteria:

- Anyone who has had a serious allergic reaction to a prior dose of hepatitis B vaccine, a component of the hepatitis B vaccine, or yeast should not receive hepatitis B vaccine.
- Those who had previous exposure to hepatitis B.
- Post liver transplant patients.
- Less than 18 years old.

5. Informed consent:

Informed consent will be obtained from all patients enrolling in the study.

References:

1. CDC. Overview and statistics of Hepatitis B. ttps://www.cdc.gov/hepatitis/hbv/hbvfaq.htm#overview
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4. Jackson S, Lentino J, Kopp J, Murray L, Ellison W, Rhee M, Stockey G et al. Immunogenicity of a two-dose investigational hepatitis B vaccine, HBsAg-1018, using a toll-like receptor 9 agonist adjuvant compared with a licensed hepatitis B vaccine in adults. Vaccine. 2017; epub.
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7. Amjad W, Alukal J, Zhang T, Maheshwari A, Thuluvath P. Two-dose Hepatitis B vaccine (Heplisav-B) results in better seroconversion than three-dose vaccine (Engerix-B) in chronic liver disease. Digestive Disease and Science July 2020.