A randomized, prospective, comparative study of the effectiveness of prophylactic entecavir treatment for HBV reactivation in past HBV infected patients with hematopoietic stem cell transplantation

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1. Protocol summary

1) **Brief Title**: Prophylactic Entecavir for HBV Reactivation in Past HBV Infected Patients With Hematopoietic Stem Cell Transplantation

2) **Study type**: Interventional

3) **Official Title**: A randomized, prospective, comparative study of the effectiveness of prophylactic entecavir treatment for HBV reactivation in past HBV infected patients with hematopoietic stem cell transplantation

2. Sponsors and Collaborators

1) **Responsible Party, by Official Title:** Investigator

2) **Investigator Information:** Dong-Gun Lee, Professor, Seoul St. Mary's Hospital,

Name of the sponsor: Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea

3) **Collaborator**s: Dong-A PharmTech Co., Ltd.

3. Study Description

1) Brief Summary

This study is a randomized, prospective, comparative study of the effectiveness of prophylactic entecavir treatment for HBV reactivation in past HBV infected patients (HBsAg-, HBcIgG+) with allogeneic hematopoietic stem cell transplantation.

2) **Detailed Description**

This study is a randomized, prospective, comparative study of the effectiveness of prophylactic entecavir treatment for HBV reactivation in past HBV infected patients (HBsAg-, HBcIgG+) with allogeneic hematopoietic stem cell transplantation.

In this study, patients are randomized into treatment group or delayed treatment group.

* Stratified randomization (Block randomization within strata) according to the presence of HBsAb at baseline was used in this study.

(1) Experimental: Treatment group (n=113)

The intervention group take entecavir 0.5mg everyday by oral administration for 3 years after allogeneic hematopoietic stem cell transplantation. The intervention group visit clinic every month and examined liver function test, HBsAg/Ab. HBV DNA level is examined at every 3 months.

* oral administration of entecavir is planned to start within 7 days after hematopoietic stem cell transplantation.

(2) No Intervention: delayed treatment group (n=113)

The delayed treatment group visit clinic every month and examined liver function test, HBsAg/Ab. HBV DNA level is examined at every 3 months. If the patient in the delayed treatment group shows HBV reactivation (positive HBsAg or HBV DNA ≥10 IU/mL), entecavir treatment is started.

4. Conditions

1) Conditions or Focus of Study: hepatitis B reactivation, hematopoietic stem cell transplantation, antiviral drug, HBV

2) Keywords: hepatitis B reactivation, hematopoietic stem cell transplantation, prophylactic antiviral agents, past HBV infection

5. Study design

1) Primary purpose: Treatment

2) Study Phase: N/A

3) Interventional Study Model: Parallel

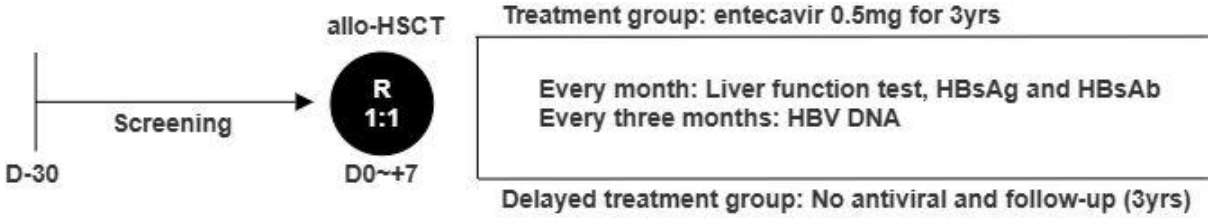
4) Number of Arms: 2

5) Masking: None (Open Label)

6) Allocation: Randomized

7) Enrollment-number of participants: 226, anticipated

8) Schematic study design



*Stratified randomization (Block randomization within strata) according to the presence of HBsAb at baseline.

- **Screening period**

  Patients will be screened based on the inclusion and exclusion criteria from up to 30 days prior to allogeneic hematopoietic stem cell transplantation (allo-HSCT) until the day of transplantation. After receiving a full explanation of the study details, written informed consent will be obtained from all participants.

- **Randomization period**

  Patients will be randomized in a 1:1 ratio to either the treatment group or the delayed treatment group between Day 0 and Day 7 following allo-HSCT. Stratified block randomization will be used, with stratification based on baseline hepatitis B surface antibody (HBsAb) status.

- **Treatment period**

  Patients in the intervention (treatment) group will receive oral entecavir at a dose of 0.5 mg once daily for 3 years after allo-HSCT. Dose adjustments will be made as appropriate based on renal function. Patients in this group will visit the clinic monthly for follow-up, including liver function tests and HBsAg/Ab monitoring. HBV DNA levels will be assessed every 3 months.

  Patients in the delayed treatment (control) group will also visit the clinic monthly for liver function tests and HBsAg/Ab monitoring, with HBV DNA testing every 3 months. If HBV reactivation occurs—defined as HBsAg seroconversion or an HBV DNA level ≥10 IU/mL—entecavir treatment will be initiated.

6) Randomization

After obtaining written informed consent, participants will be assigned a screening number. Final eligibility will be confirmed after reviewing each participant’s suitability. Eligible subjects will then be assigned a randomization number and allocated to a study group based on the predefined randomization table, which is managed by an independent third party.

Randomization will be conducted to ensure the scientific validity of the clinical trial. This process maximizes the comparability between the intervention (treatment) group and the

delayed treatment (control) group while minimizing investigator bias in subject allocation.

Randomization will be stratified by HBsAb status (negative or positive). Within each HBsAb stratum, subjects will be randomized at a 1:1 ratio to either the intervention (treatment) group or the delayed treatment (control) group, using a computer-generated scheme in permuted blocks of random sizes 2 and 4. Patients will be randomized between Day 0 and Day 7 following allo-HSCT.

The randomization sequence was generated by an independent statistician using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) at the Department of Biostatistics, Clinical Research Coordinating Center, The Catholic University of Korea, and was produced in sequentially numbered opaque sealed envelopes.

7. Arms and Interventions

1) Arms:

- Experimental: Treatment group: The intervention group take entecavir 0.5mg everyday by oral administration for 3 years after allogeneic hematopoietic stem cell transplantation. The intervention group visit clinic every month and examined liver function test, HBsAg/Ab. HBV DNA level is examined at every 3 months.

- No Intervention: delayed treatment group: The delayed treatment group (control group) visit clinic every month and examined liver function test, HBsAg/Ab for 3 years after allogeneic hematopoietic stem cell transplantation. HBV DNA level is examined at every 3 months for 3 years after allogenic hematopoietic stem cell transplantation. If the patient in the delayed treatment group shows HBV reactivation (positive HBsAg or HBV DNA ≥10 IU/mL), entecavir treatment is started.

2) Interventions:

- **Drug**: Baracle Tab (entecavir)

- **Other Names:** Prophylactic treatment group

- **Description:** The intervention group take entecavir 0.5mg everyday by oral administration for 3 years after hematopoietic stem cell transplantation.

8. Eligibility

1) Inclusion Criteria:

- Age: 19 – 70
- Patients receiving allogeneic hematopoietic stem cell transplantation
- HBV serologic test: HBsAg (-), anti-HBc IgG (+) before receiving allogeneic hematopoietic stem cell transplantation
- ECOG performence: 0-2
- patients with informed consent

2) Exclusion Criteria:

- HBV DNA (+, ≥10 IU/mL) at the time of screening
- Receiving hematopoietic stem cell transplantation from donor with HBsAg+
- Combined other chronic liver disease (severe alcoholics, autoimmune hepatitis, chronic hepatitis C etc.)
- HIV (+)
- Previous antiviral therapy history for chronic hepatitis B
- Other concomitant malignancy
- Combined autoimmune disease (rheumatic arthritis, SLE etc)
- CTP class B, C
- Decompensated complications (ascites, hepatic encephalopathy etc.)
- Active tuberculosis
- Patients with lymphoma
- Patients receiving autologous hematopoietic stem cell transplantation

9. Study population

1) Sample size estimation

At the initiation of the study in 2021, the planned sample size was 82 patients per group for both the treatment (intervention) and delayed treatment (control) groups. This estimation was based on an assumed incidence of hepatitis B virus (HBV) reactivation of 5% in the treatment group and 20% in the delayed treatment group.

The required sample size, calculated to be a minimum of 75 patients per group, was determined using a two-sample Z-test with unpooled variance, with a two-sided significance

level (α) of 0.05 and a statistical power of 80%. After accounting for an anticipated 10% withdrawal rate, the final target sample size was set at 164 patients (82 per group).

By June 2023, approximately two years after study initiation, a total of 110 patients had been enrolled (55 in each group). Among these, 17 patients (15%) had withdrawn from the study. In addition, 21 patients (19%) had died due to causes including infections and relapse of hematologic malignancy—events defined as competing risks.

Given the higher-than-expected rates of withdrawal and competing events, the sample size was recalculated based on the following revised assumptions:

The study is designed to detect the event of interest, with cumulative incidence proportions of 0.01 in the treatment group and 0.05 in the control group (a hazard ratio of 0.1951) at 3 year of follow-up period for each patient, with competing risks having cumulative incidence proportions of 0.2 in both groups at this time, and accounts for a 0.15 proportion of subjects lost to follow-up. The comparison will be made using a two-sided, two-sample logrank test accounting for competing risks with a Type I error rate (α) of 0.05 and 80% power. Using these updated parameters and the PASS version 12 software (NCSS, LLC), the recalculated total sample size was 226 patients, with 113 patients allocated to each group.

Numeric Results for a Two-Sided Test with T0 = 3 and W = 0.15

Power	N	Ctrl N1	Trt N2	Prop Ctrl p1	Hazard Ratio HR	Ctrl Main Event Incid Fev1	Trt Main Event Incid Fev2	Ctrl Comp Risks Incid Fcr1	Trt Comp Risks Incid Fcr2	Accr'l Time R	Follow Up Time T-R	Alpha	Rpt Row
0.80093	225	112	113	0.5	0.1951	0.0500	0.0100	0.2000	0.2000	3	6	0.050	1
0.80201	157	78	79	0.5	0.1615	0.0600	0.0100	0.2000	0.2000	3	6	0.050	2
0.80163	117	58	59	0.5	0.1376	0.0700	0.0100	0.2000	0.2000	3	6	0.050	3
0.80460	92	46	46	0.5	0.1196	0.0800	0.0100	0.2000	0.2000	3	6	0.050	4
0.80355	75	37	38	0.5	0.1056	0.0900	0.0100	0.2000	0.2000	3	6	0.050	5
0.80055	62	31	31	0.5	0.0944	0.1000	0.0100	0.2000	0.2000	3	6	0.050	6

Numeric Results for a Two-Sided Test with T0 = 3 and W = 0.15 (Continued)

Beta	E	Ctrl E1	Trt E2	Total Prob Event Pr(ev)	Ctrl Prob Event Pr(ev1)	Trt Prob Event Pr(ev2)	Ctrl Event Hazard Rate hev1	Trt Event Hazard Rate hev2	Ctrl Comp Risks Hazard Rate hcr1	Trt Comp Risks Hazard Rate hcr2	Rpt Row
0.19907	11.8	9.8	2.0	0.0617	0.1022	0.0211	0.0192	0.0037	0.0767	0.0748	1
0.19799	9.5	8.1	1.4	0.0714	0.1217	0.0211	0.0232	0.0037	0.0772	0.0748	2
0.19837	8.0	7.0	1.0	0.0809	0.1407	0.0211	0.0272	0.0037	0.0777	0.0748	3
0.19540	7.0	6.2	0.8	0.0903	0.1595	0.0211	0.0313	0.0037	0.0782	0.0748	4
0.19645	6.3	5.6	0.7	0.0995	0.1779	0.0211	0.0354	0.0037	0.0787	0.0748	5
0.19945	5.6	5.1	0.5	0.1085	0.1960	0.0211	0.0396	0.0037	0.0793	0.0748	6

References

Machin, D., Campbell, M.J., Tan, S.B., Tan, S.H. 2008. Sample Size Tables for Clinical Studies, Third Edition. Wiley-Blackwell, Chichester, United Kingdom.

Pintilie, M., 2006. Competing Risks: A Practical Perspective. John Wiley & Sons, Chichester, United Kingdom.

Pintilie, M., 2002. 'Dealing with Competing Risks: Testing Covariates and Calculating Sample Size'. Statistics in Medicine, Volume 21, pages 3317-3324.

10. Outcome Measures

1) Primary Outcome measure

1. Comparison of the rate of HBV reactivation between the treatment and delayed treatment groups.

Description: Comparing the rate of HBV reactivation between the treatment and delayed treatment groups during 3 years after hematopoietic stem cell transplantation * Definition of HBV reactivation: HBsAg ≥ 1.0 S/CO or HBV DNA ≥ 10 IU/mL

Time Frame: The primary outcome is evaluated during 3 years after hematopoietic stem cell transplantation

2) Secondary Outcome measure

2. Comparison of the rate of active hepatitis with HBV reactivation between the treatment and delayed treatment groups.

Description: Comparing the rate of active hepatitis with HBV reactivation between the treatment and delayed treatment groups. * Definition of active hepatitis: ALT >= 2 times of upper normal limit

Time Frame: The secondary outcomes are evaluated during 3 years after hematopoietic stem cell transplantation.

3. Comparison of the rate of hepatic failure related to HBV reactivation between the treatment and delayed treatment groups.

Description: Comparing the rate of hepatic failure between the treatment and delayed treatment groups.

Time Frame: The secondary outcomes are evaluated during 3 years after hematopoietic stem cell transplantation.

4. Comparison of the rate of survival related to HBV reactivation between the treatment and delayed treatment groups.

Description: Comparing the rate of survival related to HBV reactivation between the treatment and delayed treatment groups.

Time Frame: The secondary outcomes are evaluated during 3 years after hematopoietic stem cell transplantation.

11. Statistical analysis

Information collected from subjects of the present clinical trial are analyzed in two forms: ITT (Intention-To-Treatment) and PP (Per-Protocol)

1) ITT analysis group

The ITT population is defined as all randomized patients at the time of receiving allo-HSCT, regardless of their adherence with the entry criteria, regardless of treatment they actually received, and regardless of subsequent withdrawal from treatment or deviation from the protocol. Only some specific reasons that might cause an exclusion of a patient from the ITT population:

- No treatment was applied at all
- No data are available after randomization

2) PP analysis group

The PP population is the subset of ITT population consisting of all patients who receive and retain the treatment or follow up with test according to the study protocol for 3 years in the treatment group and the delayed treatment group, respectively. Some specific reasons that might cause an exclusion of a patient from the PP population:

- Violation of entry criteria including inclusion and exclusion criteria
- Withdrawal of consent
- Death
- B cell depletion therapy or re-transplantation following relapse of hematologic disease causing previous allo-HSCT
- Poor compliance: Discontinuation of test or drugs for 180 days or longer

In the cases of withdrawal of consent and poor compliance, their data can be used for statistical analyses until events occur.

3) Missing data handling

- Missing variables will not be imputed for planned analyses, except where otherwise specified.

4) Analysis

- The primary endpoint will be analyzed Fine and Gray competing risk survival model to estimate the subdistribution hazard ratio (SHR) and to calculate the cumulative incidence function (CIF).

- Competing risks include death, B cell depletion therapy, and due to relapse of the underlying hematologic disease that led to the initial allo-HSCT.

5) Primary and secondary endpoint analysis

- The primary endpoint will be analyzed using cumulative incidence function (CIF), as described above.
- Subgroup analyses of the primary endpoint will be conducted based on the following variables: presence of HBsAb, age, sex, underlying hematologic disease, donor type (related vs. unrelated), and ABO mismatch.
- The primary analysis population for both the primary and secondary endpoints will be the intention-to-treat (ITT) population. A subsequent analysis of the primary endpoint will also be performed in the per-protocol (PP) population.
- Sensitivity analyses will be conducted based on the time of enrollment, including comparisons between patients enrolled during vs. after the COVID-19 pandemic period and before vs. after the South Korean medical crisis.

6) Additional analysis

- Baseline characteristics of the patients were presented as mean ± standard deviation or median (range) for quantitative variables and as counts (%) for categorical variables, whichever was appropriate.
- Comparisons between the two groups were performed using a Student's t-test or Mann–Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate.
- An interim analysis of the primary and secondary outcomes will be conducted when approximately 90% of the target sample size has been enrolled and half of the planned follow-up period (1.5 years) has been completed.

12. Informed consent

Investigator and research coordinator should provide a copy of the informed consent form or any other documents shared with the subject to the subject or representative. If there are any changes to the consent form or shared documents during clinical trial, the investigator or coordinator should provide a copy of the revised form or document to the subject or his/her representative.

13. Follow-up treatment of subjects after clinical trial

After finishing clinical trial, 3 years following allogenic stem cell transplantation, the subjects are treated with standard treatment. It includes routine laboratory examinations, including liver function test, HBsAg, and HBsAb.

After completing the clinical trial—three years following allo-HSCT—participants will receive standard post-transplant care. This includes routine laboratory monitoring such as liver function tests, HBsAg, and HBsAb assessments, in accordance with institutional guidelines for long-term follow-up.