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Challenging Issues in Analysis of Chronic Hepatitis B Clinical Trials

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1. Abstract

For chronic hepatitis B (CHB) clinical trials, new challenges in the selection of the appropriate clinical endpoints were issued with the rapidly evolving concepts in designing, conducting and analyzing clinical trials. In this article, we first summarized the characteristics of different endpoints including single, composite, ordinal and multi-state endpoints related to antiviral treatment in clinical trials of CHB. Then we outlined the major endpoints of clinical trials for hepatitis B virus (HBV) cure and illustrated the corresponding statistical methods and specific considerations. We further described several new concepts on the design and evaluation of clinical trials in CHB, including adaptive design, Risk Based Monitoring and Independent Data Monitoring Committee. Multi-disciplinary and multi-level cooperation between researchers and methodological teams during the innovative clinical trials on CHB are anticipated.

2. Introduction

In recent years, the development of novel drugs for chronic hepatitis B (CHB) has received much attention, especially aiming at 'functional cure', has entered a booming period [1,2]. At the same time, new design concepts, methods, and technologies to evaluate the safety and efficacy of the novel drugs will not only shorten the process of clinical development and reduce the cost of drug development, but also increase the probability of success.

However, some critical issues such as priority target population (e.g., HBeAg status, treatment naive or treatment experienced, and with or without liver cirrhosis, etc.), therapeutic regimen (e.g., monotherapy or combination, dosage and course of treatment, etc.), outcome measures and appropriate efficacy endpoint [3]. This article will focus on the statistical considerations for analysis of CHB clinical trials.

3. Endpoints for Clinical Trials of Antiviral Therapy in CHB

3.1. Single Endpoint

In CHB clinical trials, the defining of primary endpoints is often based on the target patient population and the trial objectives. Clinical trials of antiviral therapy for CHB patients usually use a single primary endpoint. For example, at the early stage of nucleos(t)ide era two phase III trials on entecavir by Lai et al. (2006) and Chang et al. (2006), the primary endpoint was histologic improvement, which is defined as at least two points decrease in the Knodell necroinflammation score and without worsening fibrosis [1,2].

For another example, in the tenofovir disoproxil fumarate (TDF) trial by Marcellin et al. (2008) [4], both hepatitis B virus (HBV) DNA suppression (which is defined as plasma HBV DNA level of less than 400 copies per milliliter (69 IU per milliliter)) and histologic improvement are considered as the primary endpoints. With the more and more evidences demonstrated that sustained HBV DNA suppression improves liver histology and reduces the disease progression and the risk of hepatocellular carcinoma (HCC) development

[5], newer antiviral agents for CHB could get approval by demonstrating HBV DNA suppression in phase III trials. As an example, in the tenofovir alafenamide phase III trial by Buti et al. (2016), the primary efficacy endpoint was the proportion of patients with HBV DNA less than 29 IU/mL at week 48 of treatment, as determined by COBAS Taqman HBV test (Roche Molecular Systems, Inc; Pleasanton, CA, USA) with a lower limit of quantitation of 29 IU/mL and a lower limit of detection of 10 IU/mL [6].

3.2. Composite Endpoints

A composite endpoint is defined as the occurrence of any of a set of predefined events in a patient. In clinical trials with composite endpoints only the event that occurs first is accounted for. For example, the primary endpoint was time to disease progression in CHB patients, a composite endpoint including hepatic decompensation, spontaneous bacterial peritonitis, variceal bleeding, hepatocellular carcinoma, or death related to liver disease [7].

In practice, the advantages for using a composite endpoint include:

1. Providing a substantially higher overall event rate that provides adequate power with a reasonable sample size and study duration;
2. Avoiding competing risks caused by multiple endpoints. For example, patients whose first event was death would never be observed to have decompensation. If one study group had higher rates of early mortality, it could appear to have a favorable profile with respect to other endpoint events simply because fewer patients survived, diminishing the number of patients at risk for the other types of events.
3. Appropriately evaluating the efficacy of study therapy where the selection among the several endpoints is controversial. For example, in some trials, a subject who experiences any endpoint event will be switched to alternative agents. Such a change in therapy obscures the relationship between the initial study therapy and the occurrence of subsequent events, so that only the analysis of first event will be more appropriate.

3.3. New Endpoints for Cirrhotic CHB: Ordinal Outcomes and Multistate Outcomes

The composite endpoint is widely used in evaluating the long-term treatment effect on clinical outcomes of CHB patients with compensated cirrhosis (CC). However, this binary approach does not account the subsequent events occurs after the first event, therefore it could provide the whole picture of the clinical progression for patients.

In a recent study by D'Amico et al. (2020) [8], an ordinal outcome was proposed to demonstrate the treatment effect, and was validated in a cohort (2014) of untreated cirrhotic patients mostly due to HCV (Table 1) [9]. This ordinal outcome approach has a higher statistical power and requires smaller sample size in clinical trials. However, these ordered multi-category outcomes did not include HCC. This may hamper its applicability to patients with HBV-related cirrhosis, where the risk of developing HCC is still an important realistic concern despite effective antiviral therapy.

A more comprehensive clinical endpoint system for evaluating outcomes of CHB patients with CC is the multistate outcome approach, including both decompensation events and HCC. This multistate outcome model could provide more objective and accurate prognosis evaluation of the full clinical course for CHB patients with CC. Compare with a composite outcome which just accounts the events whichever occur first and ignores the subsequent events, the multistate analysis could provide a whole picture of the clinical progression for compensated cirrhotic patients. Compared with ordinal outcome which calculates odds ratio without considering the influence of time length, the multistate approach could provide hazard ratio which takes into account the time length required to the development of a certain event. However, the applicability of multistate outcome analysis in assessing the treatment effect for the prevention of disease progression in patients with CC still need further validation.

Table 1: Definition of ordinal outcomes for patients with compensated cirrhosis

States	Definition
1	Compensated cirrhosis without varices
2	Compensated cirrhosis with varices
3	Bleeding alone
4	First nonbleeding decompensating event
5	Any second decompensating event
6	Death

4. Endpoints for HBV Cure of Clinical Trials in CHB

4.1. The definition for HBV cure

As shown in (Table 2), there is a hierarchy on the definitions of HBV cure [3,10-13]. Currently, he most relevant and feasible definition is the "functional cure" of HBV which means loss of HBsAg with or without HBsAg seroconversion after a finite duration of antiviral therapy.

4.2. Surrogate Endpoints for HBV Functional Cure

Whether the endpoint of the phase II trial could be HBsAg decline or HBsAg negative conversion is still controversial. The primary endpoint of phase III trials should be functional cure; HBsAg loss in ≥30% of patients was suggested as an acceptable rate of response in these trials. Sustained virologic suppression (undetectable serum HBV DNA) without HBsAg loss 6 months after discontinuation of treatment would be an intermediate goal (partial cure). A surrogate biomarker which has been validated for prediction of sustained HBsAg loss could be considered the most appropriate criterion for the approval of new HBV assays to determine efficacy endpoints [3].

Table 2: 'Cures' in HBV and their definitions [3,10-13]

	No active disease	No replication	No reactivation	No HCC/no surveillance
Sterilizing cure				cccDNA- Integrated HBVDNA-
Complete cure			cccDNA- Integrated HBV DNA+	
Functional cure		HBsAg-cccDNA+		
Partial cure	HBVDNA- HBsAg+			

5. General Considerations in Efficacy Analysis of HBV Trials

5.1. Statistical Analysis for Single Endpoint in CHB

HBV DNA suppression rate or histologic improvement rate are usually summarized by the percentage of responses with 2-sided exact binomial 95% confidence interval (CI). The response rate and the exact 95% CI are calculated with the use of the Clopper–Pearson method.

The baseline stratum weighted difference in the proportions between the groups and its 95% CI will be calculated based on the stratum-adjusted Mantel-Haenszel proportion, where stratification factors could be oral antiviral treatment status (treatment naive vs treatment experienced) and baseline HBV DNA, among others.

5.2. Statistical Analysis for Composite Endpoint in CHB

A single statistical test is performed on the composite endpoint; consequently, no multiplicity problem occurs and no statistical adjustment is needed. Composite endpoint is commonly analyzed by using Kaplan–Meier methods, with medians and corresponding 95% CI determined according to the Brookmeyer and Crowley method with log–log transformation. Differences between events are compared by the log-rank test. The cumulative incidence of all major clinical events is assessed by *cumulative incidence function* (CIF) and displayed by Nelson-Aalen plot, where death before the estimated events is considered as the competing risk.

It is essential to clearly present the results of every specific component of a composite endpoint in study reports. These analyses will not alter a conclusion about the statistical significance of the composite primary endpoint and are considered descriptive analyses, not tests of hypotheses.

In analyzing the contribution of each component of a composite endpoint, one approach considers only the initial event in each patient, the other approach considers the events of each type in each patient.

5.3. Statistical Analysis for Ordinal Outcome in Cirrhotic CHB

Briefly, the main statistical models used in this context are extensions of the classic logistic model for ordinal response outcome [14]. They account for the category order of the outcome by grouping categories that are contiguous on the ordinal scale. There are two ordinal models: the proportional odds model and the continuation ratio model [15] .

Both the proportional odds and the continuation ratio ordinal regression models are linear and additive on the logic scale, and both use maximum likelihood methods to estimate a summary odd ratio (OR). However, different series of dichotomizations of the data, referred to as "cut-points," are used in the two models. With both models, homogeneity of effect across cut-points is assumed and a single OR summarizing the effect of interest over all cut-points is calculated.

The proportional odds model simultaneously uses all these cumulative probabilities and results in a common OR for disease progression for one group compared to the other (Table 3, left).

Other approaches not requiring proportionality of ORs have been developed [14]. Among these, "continuation ratio model" is mostly used when proportionality of ORs are not verified (Table 3, right). The continuation ratio model requires specific computational rearrangement of the original data sets as reported elsewhere [15].

Table 3: Comparison of cut points between proportional and continuation odds models based on a 6-level ordinal outcome to assess the progression of cirrhosis

Proportional Odds Model: Successive Incremental Cut Points for the Odds	Cut points	Continuation Ratio Model: Conditional Incremental Cut Points for the Odds
1 vs. 2, 3, 4, 5, 6	1	1 vs. 2, 3, 4, 5, 6
1, 2 vs. 3, 4, 5, 6	2	2 vs. 3, 4, 5, 6
1, 2, 3 vs. 4, 5, 6	3	3 vs. 4, 5, 6
1, 2, 3, 4 vs. 5, 6	4	4 vs. 5, 6
1, 2, 3, 4, 5 vs. 6	5	5 vs. 6

Note: the definition of grades is described in table 1.

5.4. Statistical Analysis for Multistate Outcome in Cirrhotic CHB

The transition of individuals through a series of distinct states is described with the multistate model. The State Transition Probability (STP) and state occupation probabilities (SOP) are usually calculated. The STP describes the probabilities of one sate progresses to other states. The SOP describes the distribution of patients' disease states at a specific time during the follow-up, given patients' disease state(s) at the beginning of follow-up. The cumulative hazards for transitions in different states of CHB patients with CC could be estimated by the Cox model with separate baseline hazards for each of the transitions. This model could specify different covariate effects for different transitions, and separate baseline transition hazards for each transition. To identify whether the effect is different across transitions, each covariate could be examined separately by the likelihood ratio test [16-20].

6. New Concepts on Designing and Conducting Clinical Trials for CHB

6.1. Adaptive Design in CHB Trials Aiming at "Functional Cure"

An adaptive design is defined as a clinical trial design that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial [21, 22]. To systematically review registered protocols of clinical trials for cure of CHB in China and abroad, clinical trials were searched on Clinicaltrials.gov and Chinese Clinical Trial Registry from inception to May 26, 2020. A total of 106 registered protocols of clinical trials for cure of CHB were included (94 in English website and 12 in Chinese website), with the number being increased over time. Most clinical trials (n = 96, 90.6%) were in phase I or phase II. The subjects of phase I clinical trials were primarily healthy individuals or treated patients, whereas the subjects of phase II clinical trials were treatment-naive patients or treated patients with viral suppression. The primary endpoint of phase I clinical trials was safety and tolerance. About half of phase II clinical trials used HBsAg loss/quantitative decline as the primary endpoint. Totally, only 3.8% (4/106) of the clinical trials used the novel design. The number of registered protocols of clinical trials for curing CHB increased over time, but most of them were in phase I or II, with few of them using novel design [23].

6.2. Risk Based Monitoring (RBM)

With the dramatic increase in the number and complexity of clinical trials, the human cost and other expenses for data monitoring are soaring. Besides, the traditional clinical trials are also vulnerable to public health emergencies such as COVID-19 endemics. Therefore, digital, remote or intelligent technologies, such as centralized Risk Based Monitoring (RBM), Optical Character Recognition (OCR) for data collection and eConsent & ePayment (2E) et al., should be actively explored and adopted in clinical trials.

In August 2013, FDA issued the guidance of "Oversight of Clinical Investigations-A Risk-Based Approach to Monitoring" to assist sponsors to monitor the clinical trials more effectively [24]. In March 2019, FDA released another guidance of "A Risk-Based Approach to Monitoring of Clinical Investigations Questions and Answers", which further expanded the methods of risk-based monitoring [25]. RBM could effectively identify the risk factors affecting the quality of clinical trials and patient rights and interests, and help to conduct risk assessment on the key steps that most likely cause problems, so as to avoid the resources waste [26].

6.3. Independent Data Monitoring Committee (iDMC)

An independent data monitoring committee (iDMC) should be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or terminate a trial [27].

In adaptive design, some adaptive adjustment are usually induced according to the interim analysis in the early stage, including eliminating invalid experimental groups, terminating clinical trials due to the observed effectiveness ahead of the schedule and re-estimating the sample size or adaptive randomization [28]. In order to avoid the test invalidity due to the leakage of interim analysis results, sponsors, researchers and statisticians should be kept blind to ensure the integrity and scientific validity of the trial. All adaptive adjustments, including whether to continue the test or not, should be determined by iDMC individually [29].

6.4. Summary and Perspective

In clinical trials of new drugs for hepatitis B, the use of new design concepts, new methods, and new technologies to evaluate the efficacy of innovative drugs is expected to shorten the clinical research process and reduce the cost. Meanwhile, the novel trial design also poses new challenges for project implementation, data management, quality control, and efficacy evaluation.

To conduct innovative clinical trials with high efficiency and high quality, close collaboration among sponsors, investigators, methodologists, supportive team and administrative sectors is required. Adhering to the principle of resource convergence, transparence and sharing, will be essential for the building of a multi-disciplinary clinical trial team of international standards. We believe this approach will facilitate the development process of novel therapy for CHB functional cure.

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