ORIGINAL RESEARCH

Preferences of Patients with Chronic Hepatitis B – A Discrete Choice Experiment on the Acceptability of Functional Cure

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Background: Current antiviral therapies for chronic hepatitis B (CHB) rarely achieve functional cure, thus often requiring lifelong therapy. A therapy achieving functional cure in a significant percentage of patients could change the treatment landscape substantially. However, the acceptability of functional cure by patients is unknown, especially if associated with additional treatment burden.

Methods: A Discrete Choice Experiment (DCE) including patients with CHB was performed between 2018 and 2019 in Germany. Patient inclusion criteria were confirmed CHB; age of at least 18 years; no history of hepatocellular carcinoma; no HIV or HCV/HDV co-infection. The final DCE included the following attributes: route of administration (oral administration by tablets; subcutaneous injection + tablets; intramuscular electroporation + tablets), side effect frequency (0/1/3 days per month), functional cure (1%/30%/50% of patients), frequency of physician visits (monthly, half-yearly) and travel time to treating physician (15/45 min).

Results: The main analysis sample consisted of 108 patients with CHB (mean age: 49.1 years, female: 37.0%, average time since CHB diagnosis: 14.0 years, 52.8% with Hepatitis B surface antigen (HBsAg) chronic HBV infection). High efficacy was found to be the main driver of decisions for/against the presented treatment options (impacted 57% of patients' decisions), followed by therapy regimen (17%), safety profile (12%) and number of physician visits (11%). Latent class analysis revealed first insights into different decision patterns, with age, gender and previous side-effect experience affecting patients' decisions.

Conclusion: In comparison to all other treatment-related attributes such as therapy regimen or safety profile, patients with CHB showed a strong preference towards a scenario where a substantial number of patients benefit from sustained disease remission, which mimics functional cure.

Keywords: hepatitis B, antiviral therapies, sustained virologic response, functional cure, discrete choice experiment, patient preferences

Introduction

Chronic hepatitis B (CHB) is a common viral infection of the liver, with serious morbidity and mortality. At the global level, recent estimates of the prevalence of CHB correspond to around 292 million people, ranging from nearly 252 million to 341 million (or 3.4–4.6% of the world population).[1–3] The overall prevalence of CHB in Europe is estimated to be nearly 0.9%, or 4.7 million.[4] Based on an analysis in 2010, CHB resulted in nearly 800,000 deaths worldwide due to subsequent liver-related diseases such as hepatocellular carcinoma and cirrhosis.[6] It was ranked among the

top 20 most common causes of death worldwide and considered as a major global health problem.[6] At the national level, the prevalence of CHB in Germany was reported to be 0.3%.[5]

Functional cure, which is defined as sustained hepatitis B surface antigen (HBsAg) loss and undetectable hepatitis B virus deoxyribonucleic acid (HBV DNA) after finite treatment duration, appears to be the optimal treatment goal of CHB.[7–10] To date, several studies have shown the benefits of HBsAg seroclearence in terms of reducing the risk of hepatocellular carcinoma following complete and sustained (off-treatment) viral suppression[11–13] and reducing the risk of cirrhosis over a long-term follow-up.[14] Key regulatory agencies such as the United States Food and Drug Administration (US FDA) and European Medicines Agency (EMA), health technology assessment (HTA) bodies such as UK's National Institute for Health and Care Excellence (NICE), and stakeholder organizations such as the Hepatitis B Foundation and the European Association for the Study of the Liver (EASL) acknowledge functional cure as an important treatment goal. In a workshop held in September 2016, in which US FDA and EMA participated, consensus was achieved on functional cure (defined as sustained loss of HBsAg) as the desirable treatment goal.[7] According to the European Association for the Study of the Liver (EASL) guidelines, in Hepatitis B e antigen (HBeAg) positive and negative patients, the ideal therapy goal is sustained off-therapy HBsAg loss (functional cure.[15,16] Please see NICE treatment guidelines on CHB treatment.[8] Please see the internet document on the positioning of Hepatitis B Foundation.[17] Current antiviral therapies for CHB, however, rarely achieve functional cure with most patients only achieving viral suppression.[18,19] Current investigations in CHB are focusing on the development of new drugs with the aim of achieving functional cure in a substantial proportion of patients, which could provide new possibilities for patients and physicians and therefore transform the CHB treatment landscape.

While clinical benefits of a functional cure in patients with CHB have been recognized, there are no data currently available on how patients evaluate future drug treatments associated with an increase in functional cure compared to characteristics of existing treatment options. In order to develop a CHB therapy preferred by patients, it is necessary to gain a better understanding of the attributes and associated trade-offs related to a CHB regimen, including the potential for functional cure. This is especially relevant if a new

therapy option would be associated with a greater chance of achieving functional cure, but had a higher treatment burden than existing therapies. In that case, patients might adhere poorly to such a therapy or even reject it altogether. This study is the first study to describe treatment preferences of patients with CHB and to estimate the relative importance of treatment attributes in a discrete choice experiment (DCE) setup.

Methods
Study Sample
This was a multicenter study conducted in Germany. Randomly selected study sites comprising outpatient gastroenterologists and hepatologists as well as eligible hospital departments located throughout the country were invited to participate. Patients were recruited via study sites. In the study sites, physicians invited the patients they treat to participate in this study if they satisfied the following eligibility criteria: a physician-reported diagnosis of CHB, at least 18 years of age, no history of hepatocellular carcinoma, no human immunodeficiency virus (HIV) or hepatitis C virus (HCV) or hepatitis D virus (HDV) co-infections, willingness/ability to participate in a 30–45 min phone interview in German language, and signing an informed consent. Excluding patients with a history of hepatocellular carcinoma, HIV or HCV/HDV ensured that the results were not confounded by any comedication or any other factor associated with these comorbidities. Patient recruitment was done via invitations by the physicians of the included outpatient and inpatient clinics.

Data Collection
All data were derived from an electronic case report form (eCRF) filled by the study site staff, and from a telephone interview with the enrolled patients. The data collected via eCRF included the information on patients' baseline characteristics (sociodemographic and general health status) and clinical data (CHB status, date of first CHB diagnosis and previous treatment, as well as current CHB treatment). Telephone interviews were conducted by trained interviewers in a computer-assisted form to assess patient preferences based on a DCE. The choice sets and related information were handed to patients by the study site staff at time of study inclusion or sent by mail a few days in advance of the actual phone interview. In addition to the DCE questions, patients were asked about their basic clinical

characteristics and socio-demographic parameters. The collected data included age, gender, marital status and occupation, as well as characteristics of previous CHB therapy. Moreover, patients were asked to provide information describing their previous and current treatment experience, which might have influenced their preferences (need of support to visit the treating physician, distance to the treating physician, experience with interferon, experience with side effects associated with CHB treatment).

Discrete Choice Experiment

A DCE is a stated preference elicitation method that has become widely accepted in healthcare research to address a wide range of health policy issues related to preferences of different stakeholders.[20] The underlying assumption of a DCE is that rational individuals will always choose alternatives with higher levels of expected utility. A DCE requires the respondents to evaluate trade-offs when deciding on different hypothetical treatment options; mirroring real-life decision-making.[21] This is important as in most cases specific treatment options are associated with certain advantages and disadvantages.[21] Specifically, our DCE analysis examined which treatment-specific attributes were preferred by respondents by asking them to make a series of binary decisions about hypothetical treatment options with different combinations of attribute levels. The main reason for applying a DCE in this study was that simply asking patients to rate treatment attributes or choose preferred items from a list generally yields no more insights than the fact that patients prefer benefits over indirect/direct costs or consequences.[20]

The DCE design of this study followed two stages. In the first stage, attributes and levels for a qualitative study stage were collected based on existing literature about patients' preferences, summary of product characteristics (SmPCs) of available CHB treatments and published clinical trial results related to current/future CHB treatments. This list of attributes (eg route of administration) and attribute levels (eg (1) tablets/(2) weekly injection) was discussed with a committee of clinical experts. Patient-friendly language with avoidance of medical terms was used. The final list was then discussed with 9 patients with CHB in extended qualitative patient interviews. Based on the dual questioning technique, these patients evaluated completeness and importance of attributes and attribute levels.

Based on the results of the qualitative study stage, four attributes were selected for stage two of the study (quantitative DCE interviews): (i) route of administration, (ii) frequency of physician visits, (iii) percentage of patients with sustained remission (mimicking functional cure), (iv) number of days per month with side effects which disrupt daily activities. For each attribute, different attribute levels were defined, presenting the range of respective attribute levels for current or future CHB treatments, determined as explained above. Table 1 presents the attributes and their levels considered in this study. Note that an attribute capturing treatment costs was not considered in this study because, in Germany, out-of-pocket costs associated with treatments are very low thanks to public health insurance and the reimbursement system.

During quantitative DCE interviews, patients were asked to decide multiple times which out of the two presented hypothetical treatment options they would prefer. Each option was set to contain all 5 attributes. The levels for each option were set to differ between option A and option B. In total, 16 choice sets were generated based on an orthogonal design.[21] To evaluate the consistency of responses, one of those sets was randomly chosen and the option A and B on it were reversed. In addition, to minimize the influence of the how the attributes are ordered in a choice set, 5 different choice sets, where attributes were the same but had a different appearance order, were generated. These sets were applied in nearly the same number of patients. The DCE cards were graphically visualized and handed to patients as a print. An example card that has been generated is presented in Figure 1.

Analyses

Patients' characteristics were described using appropriate statistical methods: categorical variables by frequency distributions and continuous variables by sample statistics (ie mean, standard deviation, median, minimum and maximum). All analyses were performed for the total DCE study population, distinguishing between patient-reported and physician-reported outcomes.

Patients with inconsistent DCE responses or incomplete DCE data were excluded from the final analysis. Preferences of the remaining patients were analyzed in a descriptive way. Furthermore, the influence of different attribute levels on the probability of a patient's decision to choose the specific choice alternative was estimated in a conditional logit regression model. This is a technique widely used to analyze the drivers of the individuals' preferences in a probabilistic framework.[22,23] It measures to what extent different treatment attributes affect the probability of choosing a treatment alternative.

Levels of the attributes can have heterogeneous effects on choices across different subgroups or "classes" of

Table 1 DCE Attributes and Attribute Levels

Attributes	Levels	Explanation Given to Patients During Interview
Route of administration	Tablet(s), up to 2x daily	Electroporation is a quick electric pulse given during injection, increasing the permeability of the cells and increasing the delivery of the drug into muscle cells. The electric pulse has a momentary mild discomfort like a "pinch-punch" at the site of infection.
	Subcutaneous injection, weekly + tablet up to 2x daily	
	Intramuscular (IM) injection with electric impulse (electroporation (EP)), 3x + tablet(s) up to 2x daily	
The frequency of visiting physicians	Monthly visits	A visit might include, eg, a blood test to check your blood values, receiving your prescription, receiving an administration of your drug or just for a general check-up
	Half-yearly visits	
Efficacy attribute (functional cure)[a]	1% of patients achieving long-term disease remission	It is the % of patients, who (after 12 months on treatment) achieve a long-term disease remission such that no further treatment is necessary. Long-term disease remission means that during treatment, the virus is completely suppressed and the viral DNA and sAg are no longer detectable in the blood – but this is also sustainable after the completion of treatment.
	30% of patients achieving long-term disease remission	
	50% of patients achieving long-term disease remission	
Safety attribute (number of days with side effects in a month)	0 days per month	Side effects can disrupt daily activities and can include. eg, Dizziness, diarrhea, tiredness, headache, back and muscle pain or joint pain, stomachache, flulike symptoms, cough, inflammation of nose and throat, nausea, feeling week, skin rash or reactions on the injections site.
	1 day per month	
	3 days per month	
Distance to treating physician[b]	15 mins	This is the commuting time required to travel to the physician.
	45 mins	

Notes: This table presents the attributes and their levels considered in this DCE. [a]Current standard of care rarely achieves function cure, which is reported for about 1% of patients within 12 months of therapy. Therefore, this level was chosen to create comparability to current medications such as interferons and oral nucleos(t)ide analogues (NUCs).[16] [b]This attribute was included to capture the interviewees' trade-offs (opportunity costs) based on a comprehensible unit of measurement.

surveyed patients. To account for this heterogeneity, a latent class model was run. Comparison of different models was achieved based on the goodness of fit (Akaike and Bayesian information criteria) to determine the optimal number of classes.[21] All statistical analyses were done using Microsoft Excel and SPSS/STATA.

Ethical Approval

This study was approved by the ethics committees of the University of Rostock (registration number: A 2018-0156, approval granted on 20.08.2018) and adhered to the guidelines of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) on DCEs.[21]

Results
Study Sample

A total of 141 patients were initially enrolled by 13 study sites, of whom 130 completed the DCE survey. Eleven

patients, although initially enrolled for the study, could not be reached by either phone or mail, or stated that they were no longer willing to participate in a phone interview. Mean age of all included 141 patients was 50.1 years, and 39.7% were female. Among them, 108 (mean age 49.1, female 37.5%) completed the DCE survey successfully without inconsistencies or missing answers. The average time since first HBV diagnosis was 14.0 years. There were no statistically significant differences in sociodemographic and clinical characteristics between patients initially enrolled and patients who successfully completed the DCE survey (Table 2).

Of the analyzed patients (n=108), 74.1% received a CHB drug therapy at time of study participation. Tenofovir was the most common CHB agent (56.5% of patients), followed by entecavir (11.1%) and lamivudine (6.5%). Previous therapy with other CHB medications was observed to be less common (25.9% of patients). Similarly,

Figure 1 Example choice card.

the use of interferons was not frequent among the patients: only 13% reported having used interferon before. Twenty patients (18.5%) reported having experienced side effects beforehand. Finally, HBsAg chronic HBV infection was observed to be the most common HBV status (52.8%) at the time of study enrollment.

Table 2 Sociodemographic and Clinical Characteristics of Patients

Variables	All Patients Enrolled		Patients Successfully Completed DCE w/o Inconsistent DCE Responses	
N	141		108	
Sociodemographic characteristics				
Mean/Median age in years (SD)	50.1/49.0	(13.3)	49.1/47.5	(13.1)
Mean/Median age at first HBV diagnosis (SD)	36.1/31.7	(15.0)	35.1/30.9	(14.1)
Mean/Median years since first HBV diagnosis (SD)	14.0/12.0	(9.3)	14.0/12.0	(9.6)
Female gender (%)	56	(39.7)	40	(37.0)
eAg status (as in EASL Guidelines)[30]				
HBeAg-positive chronic HBV infection (%)	8	(5.7)	5	(4.6)
HBeAg-positive chronic hepatitis B (%)	11	(7.8)	7	(6.5)
HBeAg-negative chronic HBV infection (%)	51	(36.2)	38	(35.2)
HBeAg-negative chronic hepatitis B (%)	70	(49.6)	57	(52.8)
HBsAg-negative (%)	1	(0.7)	1	(0.9)
Treatment characteristics				
Currently receiving medication – yes (%)	101	(72.3)	80	(74.1)
Current medication – Tenofovir (%)	71	(50.0)	61	(56.5)
Current medication – Lamivudine (%)	10	(7.1)	7	(6.5)
Current medication – Entecavir (%)	20	(14.2)	12	(11.1)
Previously received other CHB medication – yes (%)	32	(22.7)	28	(25.9)
Interferon used before – yes (%)	17	(12.1)	14	(13.0)
Interferon used before – no (%)	106	(75.2)	91	(84.3)
Interferon used before – patient does not know (%)	7	(5.0)	3	(2.8)
Interferon used before – no patient response (%)*	11	(7.8)	–	–
Experiences with adverse events/side effects				
Side-effect experience – yes (%)	23	(16.30)	20	(18.5)
Side-effect experience – no (%)	106	(75.2)	87	(80.6%)
Side-effect experience – patient does not know (%)	1	(0.7)	1	(0.9)
Side-effect experience – no patient response (%)*	11	(7.8)	–	–

Notes: Patients' sociodemographic characteristics (mean and standard deviation of age, age at first HBV diagnosis and years since first HBV diagnosis) and eAg status are based on information reported by physicians. *No patient response corresponds to patients who were initially enrolled but did not participate in phone interviews due to not being interested anymore or not reachable via phone.

Patients' Preferences Based on DCE

The estimation of the conditional logit regression model is presented in Table 3 for all 108 patients who successfully completed the interview as well as for different subgroups of patients based on gender, age (split by median age: 47.5 years) and years since first HBV diagnosis (split by median: 12 years).

In the entire group of 108 patients, functional cure, route of administration, frequency of physician visits as well as the number of days with side effects were observed to be significant predictors of a patients' hypothetical decision for or against a treatment alternative. Improvements in functional cure were positively associated with the probability of choosing a treatment alternative. The utilities associated with 50% and 30% chances of functional cure compared to 1% chance were 1.46 (p<0.001) and 0.978 (p<0.001),

respectively. Regarding the route of administration, tablets were preferred by the patients compared to the reference group of electroporation (EP) + tablets (utility: 0.430; p<0.001). The regression model showed no statistical difference between the options of EP + tablets and subcutaneous (SC) injection + tablet (0.495; p=0.06). In general, patients preferred less frequent physician visits (utility: 0.29; p<0.001) and no days with side-effects (0 days compared to 3 days: 0.30; p=0.001; 1 day compared to 3 days: 0.18; p=0.013). Patients were observed to be indifferent between a 15 versus 45 mins distance to the treating physician (utility of 15 mins compared to 45 mins: 0.07; p=0.237). Performed subgroup analyses demonstrated very similar results (Table 3).

Figure 2 shows the relative importance of each attribute on patients' choices, calculated based on the conditional logit

Table 3 Estimated Conditional Logit Regression Model for the Entire Sample and Subgroups of Patients

	All Patients (n=108)	Female (n=40)	Male (n =68)	Age > 47.5 (n=54)	Age ≤ 47.5 (n=54)	Years Since First Diagnosis > 12 (n=50)	Years Since First Diagnosis ≤ 12 (n=58)
Efficacy (functional cure) (reference group: 1% of patients with remission sustained over 12 months)							
30% of patients with remission sustained over 12 months	0.978 (0.000)	1.242 (0.000)	0.849 (0.000)	0.954 (0.000)	1.014 (0.000)	0.888 (0.000)	1.061 (0.000)
50% of patients with remission sustained over 12 months	1.457 (0.000)	1.882 (0.000)	1.248 (0.000)	1.378 (0.000)	1.548 (0.000)	1.362 (0.000)	1.545 (0.000)
Route of administration (reference group: EP +Tablets)							
Tablets	0.430 (0.000)	0.461 (0.003)	0.420 (0.000)	0.473 (0.000)	0.386 (0.002)	0.461 (0.000)	0.403 (0.001)
SC injection + tablet	0.060 (0.495)	−0.068 (0.662)	0.118 (0.267)	0.175 (0.150)	−0.064 (0.611)	0.144 (0.253)	−0.017 (0.891)
Frequency of physician visits (reference group: monthly)							
Every 6 months	0.287 (0.000)	0.285 (0.003)	0.289 (0.000)	0.207 (0.007)	0.372 (0.000)	0.315 (0.000)	0.262 (0.001)
Number of days with side effects (reference group: 3 days)							
1 day	0.182 (0.013)	0.123 (0.343)	0.215 (0.016)	0.204 (0.045)	0.160 (0.131)	0.158 (0.137)	0.203 (0.046)
0 days	0.297 (0.001)	0.269 (0.081)	0.306 (0.004)	0.241 (0.046)	0.354 (0.005)	0.258 (0.039)	0.332 (0.006)
Distance to treating physician (reference group: 45 mins)							
15 mins	0.065 (0.237)	0.122 (0.211)	0.043 (0.519)	0.012 (0.880)	0.124 (0.119)	0.069 (0.385)	0.062 (0.414)
Number of observations	3456	1280	2176	1728	1728	1600	1856
Log-likelihood	996.92	337.67	652.23	507.13	486.32	470.30	525.04

Notes: This table shows results of the analysis based on the conditional logit regression model. Shown values are utilities which do not have an own unit. P-values refer to utility differences between a specified attribute level and another reference level.

regression model. For the entire sample of patients, the efficacy attribute defined as the chance to achieve functional cure had the highest impact. This attribute influenced, on average, the decision-making to an extent of 57%. The second and third most important attributes were the route of administration (17%) and the number of days with side effects (12%), respectively. Frequency of physician visits appeared to be the fourth out of 5 attributes in terms of ranking of relative importance (11%). The least important attribute was observed to be the distance to treating physician (3%).

Generally, the relative importance of attributes in the subgroups was largely similar to the ones of the overall sample of patients and confirmed the dominant effect of functional cure in the decision-making process of patients with CHB. Small differences could be observed with regard to gender, since female patients seemed to have a stronger preference for choosing a treatment based on superior efficacy (relative importance 62% in females compared to 54% in males). Furthermore, older patients placed more importance on the route of administration than younger patients (20% vs 14%).

The latent class analysis revealed substantial differences in the importance of attributes between identified patient groups. Patients could be grouped into three main classes. In class 1 (n=50, 46.3% of patients), the importance of the efficacy attribute was substantially higher than in the main sample (77% importance). In class 2 (n=39, 36.1%), patients' preferences were characterized by an almost equal importance of several attributes, with frequency of required physician visits (30%), safety profile (27%) and efficacy (22%) driving 79% of the hypothetical decisions. In contrast, a small group of patients within class 3 (n=19, 17.6%) did not attach importance to efficacy (2%) or number of physician visits (1%), but instead would choose a treatment mainly based on the route of administration (71%) (Figure 2).

Bivariate logistic regressions were run to investigate the association between falling into one of the identified preference classes and observed patient characteristics. At a 10% significance level, having previous side-effect experience was found to be a determinant of the probability of belonging to class 2 (class of patients for whom safety profile was considered more important; odds ratio
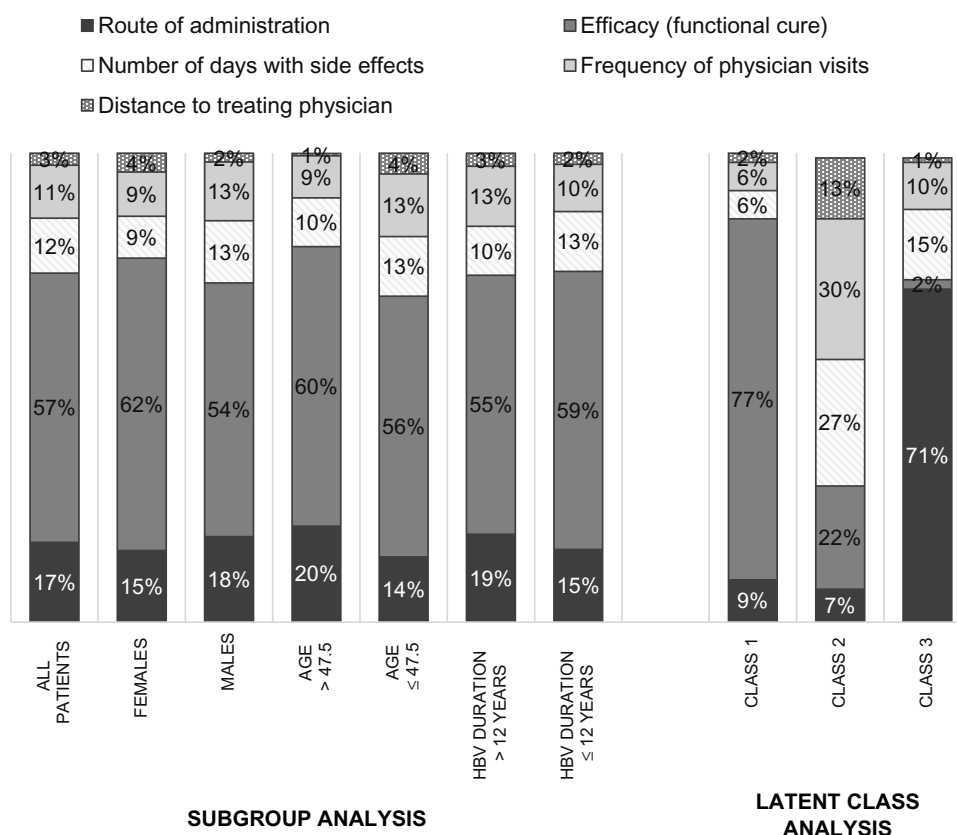
Figure 2 Relative importance of each attribute for patients' hypothetical treatment choices (entire sample and 6 subgroups).

(OR)=2.62; p=0.057). In addition, an older age was found to be a significant determinant of the probability of belonging to class 3 (class of patients for whom therapy regimen was more important than efficacy and other attributes; OR= 1.04; p=0.034).

Based on the results from the conditional logit model for the overall sample, final overall utilities for different hypothetical treatment options were estimated (Figure 3). A treatment characterized by EP + tablets as route of administration, a 50% functional cure probability, a side
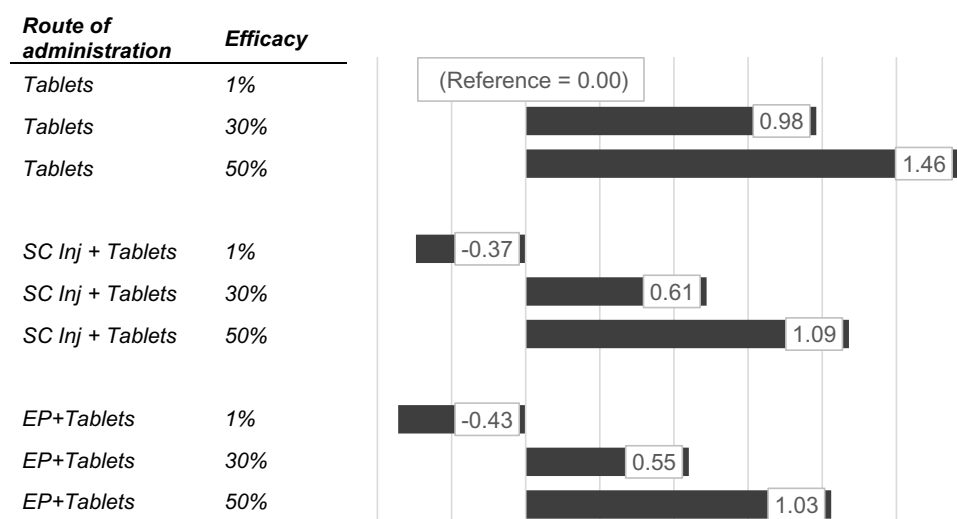

Figure 3 Relative utility associated with different treatment options (fixed attribute levels: 1 day with side effects, half-yearly physician visits, 15 mins of travel time to physician).

effect risk of 1 day per month, and physician visits every 6 months was associated with an additional utility of 1.03 in comparison to a treatment regimen that can be described by a 1% chance to reach functional cure, a tablet regimen only, a side effect risk of 1 day per month, and physician visits every 6 months. As the latter describes currently available antiviral therapies such as nucleoside/nucleotide analogs (NUCs), the above results show that the first hypothetical treatment would be associated with a higher utility from a CHB patient perspective.

Discussion

This study aimed to describe preferences of patients with CHB over different attributes in a DCE setup. Based on a conditional logit model using a sample of 108 patients, it was found that the main driver of decisions for/against treatment options was the level of functional cure a treatment can achieve (impacted 57% of patients' decisions), followed by therapy regimen (17%), safety profile (12%) and number of physician visits (11%).

To our knowledge, characteristics of CHB populations in Germany have rarely been analyzed so far, which makes it difficult to compare patient characteristics in our study to previous research. At the European level, in terms of gender distribution, a surveillance study on Hepatitis B epidemiology conducted in 2017 reported a 1:1.6 female/male ratio.[24] This aligns with the gender composition of the patient samples in our study (patients initially enrolled, 1:1.52; patients who completed the DCE, 1:1.67). In terms of age distribution, there were differences between this study and ours, which could be due to several reasons ranging from different inclusion/exclusion criteria, to the fact that our study focused on Germany only. However, our age distribution (mean age 49.1 years) was in line with another survey of patients with CHB in Singapore, which reported a mean age of 47 years.[25]

Several studies investigated patients' and physicians' preferences over treatment alternatives for different hepatitis types. For example, studies focusing on hepatitis C treatments showed a variety of outcomes (sustained viral response, treatment frequency, therapy duration) to be important from the perspective of patients and physicians.[26–29] Similar to our results, these studies found long-term efficacy outcomes as the most important drivers of patients' and physicians' preferences. Nevertheless, to the best of our knowledge, there is a lack of studies investigating patient preferences regarding CHB treatment. Only

one study conducted among 421 patients attending a CHB follow-up clinic in Singapore could be identified in this respect. This study reported that 77.5% of the patients would choose the most effective drug regardless of cost, and most patients preferred oral routes of administration over other therapy regimens.[25] Although there are differences in study designs (eg efficacy was defined by functional cure in our investigation and no costs were included in our study due to the general reimbursement system in Germany), these findings largely align with ours in terms of the general conclusion that long-term efficacy is clearly preferred by patients, and that patients favor tablets as the preferred route of administration.

Our latent class analysis revealed that the majority of patients look at functional cure when deciding about a CHB treatment. However, a minority (about 18%) primarily considers the route of administration when making a decision for or against a treatment. Due to small sample sizes, we were not able to describe this minority of patients in terms of their characteristics even if older age seemed to be a predictor for belonging to this class. Some unobserved characteristics not documented in our eCRF and patient interviews might also be predictors in this respect.

Strengths

The main strengths of this study are the robust methodology to elicit preferences that included taking into account trade-offs the patients made derived from qualitative patient interviews, a multicenter sample of patients with CHB that was described regarding its clinical characteristics by treating physicians, and relying on phone interviews with trained interviewers instead of anonymous online questionnaires.

In addition, modelling patients' decisions via a conditional logit model ensured that all patient-level characteristics invariant across a patients' choices such as their past experiences in terms of treatment duration or cognitive characteristics are taken into account. That is, any characteristic that is not changing across patients' choices were controlled within this analysis. Also, having patients enrolled via multiple study sites throughout Germany meant that the risk of any potential study site or regional bias was taken into account.

In terms of findings, our study is the first DCE investigating the preferences of patients with CHB. Moreover, it is the first study estimating the patient-reported importance of functional cure, which was already considered a key endpoint for clinical research.[7,30] This is important as current CHB treatments mainly achieve viral suppression

as long as patients continue therapy, and functional cure is rarely achieved.[18,19] However, a finite treatment duration brought by functional cure could result in better medication adherence, which is key for treatment effectiveness, as well as being a regular concern in the current therapy.[31] In addition, finite therapy might improve the overall safety of CHB treatment, since no lifelong exposure to antiviral therapies would be necessary anymore.[32]

Our study shows that patients demand such a treatment, almost irrespective of the associated treatment burden.

Limitations

We acknowledge some limitations of our analysis. First, a DCE is a complex way of collecting information from the perspective of the patients. To minimize potential biases that can emanate from the complexities of the DCE, the interviewers had been trained ahead of the interviews. In addition, interviewers acted accordingly to an interview guideline and were trained to comply with it. Patients received information on the study objectives and an extensive explanation of attributes and attribute levels as well as colored printouts of the DCE cards to increase the understandability of the DCE itself.

Second, our data collection did not explore patients' country of origin. It was shown that the risk of CHB is nearly 4.3 times higher in patients with a migration background than natives in Germany.[30] Thus, the authors also expect a certain percentage of the patients participating in this study to have a migration background. Nevertheless, the results presented in this study would still represent the preferences of patients treated in Germany irrespective of ethnic background, and therefore cultural and ethnic background was not investigated further in this study.

Third, our attribute levels mirrored real-life treatment alternatives in only simplified terms. This is a methodological limitation associated with all DCEs. Furthermore, the number of attributes and attribute levels that can be presented to patients in a DCE is limited.[22,33] To deal with this limitation, the attributes used within the quantitative DCE stage were chosen based on qualitative discussions with patients using the dual questioning technique so that the reported attributes represented the most important from a patient perspective.

Fourth, even if patients receive extensive written information and explanations by the interviewers, there is a remaining risk that patients might not have understood specific attributes included in the DCE (eg application of drugs by EP). We tried to minimize the bias resulting from this by excluding all patients who provided inconsistent DCE responses, as identified by the provided treatment choices in response to an included test card.

Fifth, statistical power could not be reached for some of the performed analyses due to the limited number of patients, especially for subgroup analysis and latent class analysis. Nevertheless, first indicators for specific patterns could be revealed, and further research within a broader CHB population is needed to confirm our findings. In this respect, it would also be interesting to repeat our DCE design in other countries and within other health-care systems as our study focuses on a German population.

Sixth, the main purpose for inclusion of travel time to treating physicians was to use the travel time as a unit to express patient preferences. However, this would have required a significant utility difference between the chosen attribute levels (15 versus 45 mins). In our DCE, however, such a significant utility difference could not be observed so we could not use results on this attribute for the original purpose.

Finally, the difference in upper and lower levels of the presented attributes might themselves have influenced patients' decisions for or against a specific treatment alternative. However, the attribute levels presented to patients were not randomly chosen but presented as current and potential future therapy options, as described in SmPCs or clinical trial publications.

Conclusions

Key regulatory agencies, HTA bodies, patient organizations, as well as medical and health-care professionals' associations call for the need to achieve functional cure in a significant percentage of patients with CHB. Therefore, current research is aiming to develop curative and innovative treatments in order to address unmet needs of patients with CHB and thereby significantly transform the therapy landscape.[7,34,35] Our study shows that the chance to increase the rates of "functional cure" is clearly preferred by patients with CHB compared to life-long therapy regimens, even if the latter might be associated with a lower treatment burden.

Ethical Approval and Informed Consent

The study was approved by the ethics committees of the University of Rostock and adhered to the ISPOR guidelines on discrete-choice experiments. All patients signed an informed consent.

Author Contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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