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TUTORIAL

Design and conduct considerations for studies in patients with hepatic impairment

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Abstract

Despite the liver being the primary site for clearance of xenobiotics utilizing a myriad of mechanisms ranging from cytochrome P450 enzyme pathways, glucuronidation, and biliary excretion, there is a dearth of information available as to how the severity of hepatic impairment (HI) can alter drug absorption and disposition (i.e., pharmacokinetics [PK]) as well as their efficacy and safety or pharmacodynamics (PD). In general, regulatory agencies recommend conducting PK studies in subjects with HI when hepatic metabolism/excretion accounts for more than 20% of drug elimination or if the drug has a narrow therapeutic range. In this tutorial, we provide an overview of the global regulatory landscape, clinical measures for hepatic function assessment, methods to stage HI severity, and consequently the impact on labeling. In addition, we provide an in-depth practical guidance for designing and conducting clinical trials for patients with HI and on the application of modeling and simulation strategies in lieu of dedicated trials for dosing recommendations in patients with HI.

INTRODUCTION

The clearance of a drug and its metabolite(s) from the body is the sum of multiple processes that encompass both metabolism and excretion. There are several sites of metabolism with the liver being the primary site. Hepatic impairment (HI) can impact the safety of a drug by the accumulation of the drug or its metabolites in toxic concentrations or impact the efficacy of a drug (i.e., through suboptimal conversion to the bioactive form, resulting in the need for a dose adjustment in these patients). It is therefore important that the impact of varying degrees of HI on the pharmacokinetics (PK) of a new drug and its metabolite(s) be investigated to be able to define a safe and efficacious dose for these patients.

The liver can clear a drug through various biotransformation mechanisms and/or through biliary excretion. Details on drug metabolism in the liver have previously been reviewed.[1]

HI can include alterations in the expression and activity of hepatic transporters and metabolizing enzymes as well as reduced duodenal cytochrome P450 (CYP)3A expression and activity.[2,3] Age, gender, nutritional status, (co-)medications, genetics, and disease state are some of the factors that may affect hepatic function.[1,4] Multiple chronic disease conditions which destroy the liver parenchyma may ultimately lead to hepatic and biliary

cirrhosis.[5] Hepatic blood flow, hematocrit, plasma protein binding, functional hepatocytes, and biliary excretion are all affected in liver cirrhosis.[5] The effect of liver dysfunction on PK processes such as absorption, distribution, and elimination has previously been reviewed.[6]

Important to note is that HI affects multiple systems in the body and can also lead to impaired renal function.[7] The reader is referred to a recently published tutorial for more information on studies in patients with impaired renal function.[8] The current tutorial aims to provide an overview of the global regulatory landscape and practical guidance for successfully designing and conducting clinical HI trials. An HI study evaluates the effect of varying degrees of hepatic dysfunction (mild, moderate, and severe) on the PK of a drug and its active metabolite(s). The tutorial will also discuss the applicability of various modeling and simulation methods to either guide the need for a dedicated study and/or its design and the applicability of modeling and simulation as an alternate method.

GLOBAL REGULATORY LANDSCAPE

The US Food and Drug Administration (FDA) published guidance in May 2003 on the conduct of PK studies in patients with HI.[9] In August 2005, the European Medicines Agency (EMA) provided a guidance for PK evaluation of medicinal products in patients with HI.[10] No specific guidances by other major regulatory authorities are available and it the authors' experience that most of the regulatory agencies reported to follow either the FDA guidance or the EMA guidance on their recommendations of when and how to assess the effect of HI on the drug PK. A comparison of the key guidelines for HI studies as per FDA and EMA guidances is presented in Table 1 and summarized below.

In addition to the background about the importance, the scope, and the timing of the PK study in patients with HI, the FDA and the EMA guidances provide guidelines on the design, the conduct, and the analysis of HI studies and how to interpret the findings of these studies to support dosing and labeling recommendations. In general, the two guidances are very similar and generally follow the same structure of when the HI studies should be conducted, the study design considerations, and the recommendations on data analysis and labeling issues.

The FDA guidance and EMA guideline acknowledge the need to assess the effect of HI on a drug's PK if the PK or PD of the drug and/or its active metabolites are altered in patients with HI to the extent that a dose adjustment is needed in these patients.

Specifically, the FDA guidance recommends a PK study in subjects with HI if hepatic metabolism accounts for a substantial portion of the elimination of a parent drug or active metabolite (>20% of the absorbed drug). Similarly, the EMA guideline recommends a PK study in subjects with HI if HI is likely to significantly alter the PK of the drug and/or its active metabolites. However, unlike the FDA guidance, the EMA guideline does not recommend a specific cutoff value for hepatic metabolism. While the EMA guideline recommends a study when the drug is likely to be used in patients with impaired hepatic function, the FDA guidance does not clearly outline the use of drug in HI patients as a consideration to assess the need for a PK study. In addition, the FDA guidance recommends a dedicated HI study for narrow therapeutic range drugs even if <20% of the absorbed drug is eliminated via the liver, and for drugs with unknown metabolism.

Unlike the EMA guidance, FDA guidance has specific recommendations on when the HI study is not needed (renally excreted drugs and gaseous or volatile drugs that are drugs excreted via the lungs). In addition to conducting a dedicated stand-alone HI study, the regulatory agencies recognize the use of population PK (popPK) analysis to assess the effect of HI on the PK of the drugs if patients with HI have not been excluded from phase II and phase III studies (some studies exclude patients with elevated bilirubin, aspartate aminotransaminase [AST], or alanine aminotransferase levels or low albumin levels for safety reasons) and enough PK samples have been collected in these studies. While both the FDA and EMA guidances propose the popPK approach to assess the effect of HI, EMA also recognizes the use of physiological-based pharmacokinetic (PBPK) models for estimating the effect of HI on drug PK which can be used to optimize HI study design. The use of modeling and simulation approaches in the assessment of the effect of liver function on drug disposition is discussed more in the section in this tutorial on the application of modeling and simulation tools to assess the impact of HI on drug PK.

Both guidances[9,10] recommend using the Child–Pugh classification for the categorization of subjects with HI. However, both regulatory agencies have acknowledged that the Child–Pugh classification was not specifically designed to determine the drug elimination capacity of patients with HI and proposed alternative classifications that may be appropriate for this purpose. In addition, the guidances point at the development of new classification methods to predict dosing adjustment needed in subjects with HI in the grand scheme of drug development. However, until an optimal classification system is available, the FDA and EMA recognize the Child–Pugh classification as the most appropriate method of HI classification and it is adequate to continue using the Child–Pugh classification in a dedicated HI study.[9–11] The liver function classifications system is discussed in more detail in the section on the assessment of hepatic function in this tutorial.

TABLE 1 Comparison of the key guidelines for a hepatic impairment study as per Food and Drug Administration and European Medicines Agency guidance

Guideline topic	EMA guidance	FDA guidance
Factors affecting components of Child–Pugh classification system	Guidance indicates that liver disease may alter the albumin and PT in general. However, no such explicit details mentioned in the guidance	Guidance explicitly quotes that the components of Child–Pugh classification system (bilirubin, albumin, prothrombin, encephalopathy, and ascites) should not be altered by underlying comorbidities such as metastatic cancer, hypoalbuminemia, encephalopathy ascites
Alternative approach: Assessment of impaired metabolic capacity	In addition to Child–Pugh scoring, EMA guidance has laid out alternative approaches such as use of CYP3A4 probe drug as 'positive control' given if investigational drug is CYP3A4 substrate	No such details mentioned in the guidance
Alternative approach: Assessment of hepatic drug elimination mechanisms	Guidance recommends the use of exogenous marker in parallel with Child–Pugh classification particularly to assess the mechanism of hepatic drug elimination (e.g., antipyrine, MEGX [lidocaine metabolite], ICG [indocyanine green], and galactose)	No explicit information on utilization of exogenous markers to investigate mechanisms of hepatic drug elimination
Use of historical control	EMA discourages the use of historical control instead of including a within-study control with normal hepatic function	No such explicit details mentioned
Drug-specific characteristics: Protein binding	For the drug/metabolites with high protein binding, guidance recommends analyzing and describing the PK of unbound concentrations of the drug. No limit indicated with regards to fraction unbound for the highly protein-bound drugs	Clear and explicit language for the PK assessment of drugs that extensively bind to plasma protein. The guidance recommends that the unbound fraction be determined at least at trough and maximum plasma concentration. The clearance and volume parameters are appropriately expressed in terms of both unbound and total concentrations of drug in plasma/serum/blood. As per guidance, the drugs with *fraction unbound <10%* are classified as highly protein-bound
Drug-specific characteristics: Extraction ratio	No limit indicated for the extraction ratio, a drug-specific property	The guidance indicates that drugs with an *extraction ratio >0.7* are highly extracted by the liver and should have the similar PK assessment considerations as mentioned above for high protein-binding drugs
Number of subjects	The guidance quotes that number of subjects enrolled should be sufficient to detect clinically relevant PK difference. No information is indicated on the number of subjects	The guidance indicates a minimum of *eight subjects* to be necessary to be enrolled in the control and moderate impairment arms

Abbreviations: CYP, cytochrome P450; EMA, European Medicines Agency; FDA, Food and Drug Administration; PK, pharmacokinetics; PT, prothrombin time.

ASSESSMENT OF HEPATIC FUNCTION

Currently, two methods are generally used to stage liver function in PK studies in subjects with HI. Child–Pugh criteria and National Cancer Institute (NCI) Criteria. Child–Pugh is the recommended method in FDA and EMA regulatory guidance. It was introduced in 1964 by Child and Turcotte[12] and was modified by Pugh and his group in 1972.[13] The method was originally designed to predict mortality during surgery and it is now used to determine the prognosis of cirrhosis and the need for liver transplantation. It uses three liver laboratory assessments (total bilirubin, serum albumin, and International Normalization Ratio [INR]) and two clinical measures associated with liver disease (ascites and hepatic encephalopathy). Each measure is given a score from 1 to 3 (Table 2) and the corresponding scores for all measures are added to classify the subjects into: mild (score 5–6), moderate (score 7–9), or severe (score 10–15) HI.

The NCI criteria were developed by the Organ Dysfunction Working Group[14] to guide chemotherapy dosing for NCI-sponsored clinical trials. It uses two liver laboratory measures (total bilirubin and aspartate aminotransferase) to stage HI as shown in Table 3. The method

TABLE 2 Child–Pugh criteria for staging liver impairment

Measure	1 point	2 points	3 points
Bilirubin, mg/dl	<2	2–3	>3
Serum albumin g/dl	>3.5	2.8–3.5	<2.8
International normalized ratio	<1.7	1.7–2.3	>2.3
Ascites	None	Mild	Moderate to severe
Hepatic encephalopathy	None	Grade I–II	Grade III–IV

TABLE 3 National Cancer Institute criteria for staging liver impairment

Group liver function	Group A normal	Group B mild	Group C moderate	Group D severe
Total bilirubin	≤ULN	B1: ≤ULN B2: >1.0×–1.5× ULN	>1.5×–3× ULN	>3× ULN
AST	≤ULN	B1: >ULN B2: Any	Any	Any

Abbreviations: AST, aspartate aminotransaminase; ULN, upper limit of normal.

is mainly used in studies evaluating the PK of anticancer drugs in cancer patients. Outside of oncology, Child–Pugh is the main system used.[15]

CLINICAL HI STUDY DESIGN

The HI study design is primarily intended to compare the drug PK in subjects with HI to the subjects with normal liver function. Therefore, prior PK information on the drug will help in the study design and the interpretation of the results of the HI study. With regards to the HI study design, full and reduced study designs have emerged as possible designs (Figure 1). A full study design requires enrollment of subjects in all three Child–Pugh categories (mild, moderate, and severe), as well as subjects with normal hepatic function. In this study design, at least six subjects in each group are needed, as per regulatory guidance, to support specific dosing recommendations for all HI subjects. A reduced study design can be used to assess the effect of HI on drug exposure. In this design, the regulatory agencies recommend comparing the PK of the drug in subjects with moderate HI to subjects with normal liver function with at least eight subjects in each group. Results from this study would guide the dosing recommendations or the need for further assessment in subjects with mild or severe HI. The FDA[9] advises that the findings in subjects with moderate HI in a reduced design study would be applied to subjects with a mild HI, and dosing in subjects with severe HI would generally be contraindicated. However, the EMA guidance[10] recommends that if a significant effect is detected in the moderate HI group, the PK in subjects with milder and, if possible, more severe degrees of impairment need to be evaluated to propose dose recommendations for these groups.

In addition to the full and reduced study design, the regulatory agencies recognize popPK analysis in the target patient population enrolled in phase II or phase III clinical studies as an acceptable approach to assessing the effect of HI on the PK and, in certain circumstances, the safety of the drug. This analysis may also be used to confirm that no dosage adjustment is necessary, in case of the absence of significant effects on PK of subjects with HI.

Generally, subjects with varying degrees of HI are enrolled in HI studies. However, for certain toxic drugs without adequate safety margin for evaluation in otherwise healthy subjects, only subjects from the intended patient population can be enrolled in these studies, because of ethical concerns regarding short- and long-term safety of these agents.[16] For instance, the effect of HI on the exposure of anticancer drugs like niraparib and osimertinib were evaluated in a dedicated HI study where single-dose PK was conducted in cancer patients with varying degrees of HI.[17,18] In some cases, a phase I study to compare the safety and exposure of the anticancer agents in patients with varying degree of HI following multiple-dose administration was conducted to identify a safe dose in this subgroup of patients.[19–23] However, this phase I study design is still uncommon and limited to oncology drug development because of the high risk of developing hepatotoxicity for many anticancer agents and the potential for liver metastasis.[24]

To be eligible for enrollment in the HI study, subjects with HI are required to have stable HI, defined as no clinically significant change in disease status within a certain time (at the discretion of the investigator) before screening. In addition, subjects with HI often have comorbidities such as diabetes and hypertension. To avoid narrow eligibility criteria and to shorten the timeline of the HI study, investigators may allow the enrollment of subjects with HI with comorbidities/concomitant medications who have stable disease and are under medical control.

Generally, subjects with a history of malignant diseases, an immunocompromised status, an abnormal electrocardiogram at screening, or a current or recent history of drug

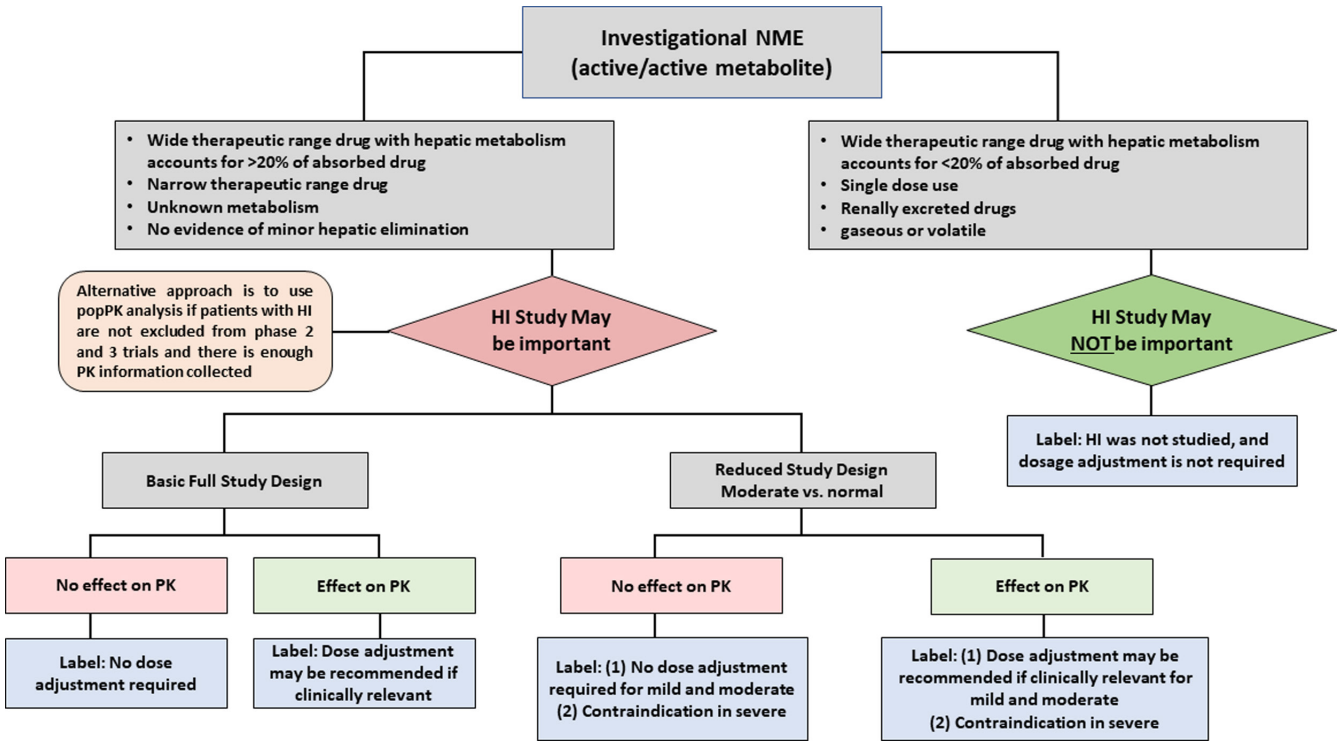

FIGURE 1 Decision tree for conducting a hepatic impairment study and impact for labeling. HI, hepatic impairment; NME, new molecular entity; popPK, population pharmacokinetics

or alcohol abuse are excluded from the HI study for safety reasons. Also, for an orally administered drug, subjects with gastrointestinal disorders will likely be excluded from the HI study. Overall, additional enrollment eligibility criteria and study design elements in each HI study might be considered based on specific drug features (protein binding, metabolizing pathways, drug transporters profile, solubility, etc.), activity, and safety profile. For instance, as per FDA guidance, for the drugs/metabolites that exhibit a high extent of protein binding (i.e., unbound fraction <10%), additional PK considerations in the study design such as sampling plan and bioanalytical methods should be kept in mind. For such drugs/metabolites, the study should be designed to determine the unbound fraction at least at trough (last measurable concentration) and at the maximum plasma concentration. The PK estimates, like clearance and volume of distribution, should be appropriately expressed in terms of both unbound and total concentrations of drug in plasma/serum/blood. Similar study design considerations to account for protein binding should be followed while assessing the PK of the drugs that are highly extracted in the liver (i.e., extraction ratio >0.7) in HI patients.

Subjects enrolled in HI studies are often vulnerable to polypharmacy due to underlying comorbidities. Depending on the metabolic pathway, these concomitant medications might interact with the investigational drug and should be avoided during the study. However, subjects on a stable dose of medication and/or treatment regimen with available information to exclude potential interaction might be enrolled in the HI study. Therefore, the HI study should be carefully designed to enhance enrollment and avoid any potential disease or drug interactions.

In addition to reporting the disease status and any concomitant medications, laboratory test results for serum bilirubin, serum albumin, prothrombin time (PT), and the stage of hepatic encephalopathy with or without ascites should be done during the screening period of the HI study to determine the Child–Pugh score.

A single-dose PK study is used in most cases while a multiple-dose study with the determination of the PK at a steady state might be used in some cases where the PK of the drug and potential active metabolites exhibit nonlinearity and a time-dependent PK profile over the clinical dose range.

In the HI study, the administered dose is in general the same as the clinical therapeutic dose. However, a reduced dose may be needed in HI patients if there are concerns about the drug safety at higher blood levels. The route of drug administration should be the same as that intended for the clinical use of the drug; and if more than one route is available, the route that provides maximum information regarding the impact of HI while maintaining the sensitivity to the drug's elimination should be used (e.g., oral versus topical).

The control group of subjects with normal hepatic function should be matched to the HI subjects with respect to age, gender, and weight. There are no recommendations in the regulatory guidances about the matching procedure,

but two matching approaches are commonly used, being (1) 'individual matching', in which control subjects are matched to subjects with HI on a one-by-one basis for each of matching criteria and (2) 'group matching', in which a subject with normal hepatic function will be selected based on the distribution (mean, median, or percentile) of each matching criterion to subjects with HI. In addition to the matching criteria, other factors that can potentially affect drug PK should be considered such as smoking, alcohol intake, concomitant medications, and ethnicity/race.

An adequate sampling plan to assess the PK profile of the parent drug and any active metabolites in subjects with different degrees of HI must be used in the HI study. For example, enough sampling points should be added to the terminal phase of the PK profile if the clearance of the drug is expected to be slower in subjects with HI to adequately estimate the PK parameters in these subjects. Furthermore, if the drug demonstrates a high extent of plasma protein binding, the protein binding should be assessed in different HI groups and the PK should be described for the total and unbound concentrations.

DATA ANALYSIS FOR ASSESSING THE EFFECT OF HI

The recommendation for dosing in patients with HI is based on the understanding of the relationship between the measures of HI and relevant PK parameters.

Step 1 Estimation of PK parameters

As with all PK studies, plasma concentration data of the drug and active metabolite(s) obtained in the HI studies are used to estimate PK parameters, using noncompartmental analysis. In addition, urinary excretion data, if collected, may also be analyzed. The key PK parameters estimated in HI studies include apparent clearance (CL/F), renal and non-renal clearance (CL_R and CL_{NR}), apparent volume of distribution (Vd/F), elimination half-life ($t_{1/2}$), as well as exposure parameters such as the area under the plasma concentration–time curve (AUC) and maximum plasma concentration (C_{max}).

Step 2 Modeling the effect of different degrees of HI on the PK of the drug

This step in the data analysis involves the development of mathematical models that can quantitatively relate the change in a specific PK parameter (such as total body clearance, oral clearance, apparent volume of distribution, unbound clearance), or dose-normalized area under the unbound concentration–time curve of the drug (or active metabolite) with hepatic functional abnormalities (e.g., hepatic blood flow, serum albumin concentration, PT, or overall impairment scores such as Child–Pugh).[9] PopPK analysis, using nonlinear mixed-effects modeling and covariate analysis, can also be used to determine the impact of HI on the parameter of interest. Models can use the HI score (i.e., Child–Pugh) as a categorical variable. Alternatively, regression analysis can be used, where the hepatic functional abnormalities as described above and PK parameters are continuous variables. The latter approach is the preferred method from an analytical perspective.[16] In addition, other approaches such as mechanistic modeling (i.e., PBPK) can be used if adequately supported as outlined in the EMA guidance.[10] More details on the use of modeling approaches are explained in the section in the tutorial on the application of modeling and simulation tools to assess the impact of HI on drug PK.

The estimated results should include the model-predicted PK parameter estimates as well as measures of their precision (i.e., standard error or confidence interval) and, in addition, the prediction error estimates of drug/active metabolite clearance (such as confidence bounds for the prediction estimates) over a range of defined hepatic functional abnormalities.

Step 3 Making dosage recommendations based on PK changes

Dose adjustment recommendations in patients with specific degree of HI should then be developed using (a) the model in the previous step and (b) the exposure–response relationship. In general, the goal is to achieve drug exposure (e.g., AUC or C_{max}) in patients with HI that is comparable to that observed in subjects with normal hepatic function. A review article showed that dose adjustments in patients with HI were in general inversely proportional to observed changes in PK and aimed to achieve comparable exposure to subjects with normal hepatic function.[16]

To determine whether a dose recommendation is needed, a confidence interval approach, rather than a significance test, is preferred.[9] According to the FDA HI Guidance,[9] if the effect of HI on PK is obvious (e.g., ≥2-fold increase in AUC), a dose adjustment may be included in the label. However, the exposure–response relationship should guide the decision for dose adjustment. As such, a drug which showed 50% increase in exposure in subjects with HI should have a dose adjustment recommendation in this subgroup if 50% increase in exposure is expected

to translate into a clinically meaningful increase in adverse events. For example, a 50%/32% increase in ribociclib C_{max}/AUC in patients with moderate HI led to a dose adjustment in this subgroup (400 mg q.d. instead of 600 mg q.d.).[25] If the exposure increase observed in HI subgroups is deemed not clinically important, this would need to be supported via exposure–response analyses. Ways to derive a dose recommendation for HI can be by exposure-matching (HI systemic exposures fall within the 5th and 95th percentiles of the reference group) or to match the confidence interval of the mean effect to a predefined no-effect boundary.[26] An alternative approach could be leveraging the modeling and simulation to determine the hepatic function threshold below which dosing adjustment is recommended.

IMPACT ON LABELING

The FDA[9] and EMA[10] guidances summarize which information is required to be incorporated in the label (Figure 1). It is specifically stated that the dose recommendations in the label should also point out if HI does not change the PK of a drug. Details of the results of the HI study and its clinical relevance to drug usage in patients with different degrees of HI are presented in the PK subsection of the Clinical Pharmacology section of the drug label (Section 4 in the EU Summary of Product Characteristics and Section 12 in the US Prescribing Information).[27,28] For drugs with specific dosage recommendations in different subgroups of patients with HI, the information is included in other relevant sections of the label such as 'Use in specific populations', 'Dosage and Administration', 'Warnings and Precautions', and 'Contraindications'.

APPLICATION OF MODELING AND SIMULATION TOOLS TO ASSESS IMPACT OF HI ON DRUG PK

Population pharmacokinetics modeling in HI studies

Model-informed drug development has been increasingly adopted in the past two decades to represent a cornerstone in risk/benefit evaluations and supporting drug labeling across several health authorities. PopPK typically applies a nonlinear mixed-effects model to evaluate the correlation between various covariates (age, weight, gender, and measure of organ function) and systemic drug exposure. The use of popPK approaches is important when a dedicated HI study in a certain subgroup (e.g., subjects with moderate or severe HI) has not been conducted or completed, for example, when the safety profile does not support conducting a dedicated study in otherwise healthy subjects. In such a case, data from phase I/II/III clinical studies in patients could be utilized to evaluate the effect of HI. Since PK sampling in these studies is typically sparse and does not allow for noncompartmental PK analysis, these types of data lend themselves to popPK approaches. Further, the number of patients included in these clinical studies for the mild HI category is typically larger than that in the dedicated study (i.e., 6–8 patients). The main limitation of this approach is that in many cases the clinical studies exclude with higher degrees of HI (e.g., moderate and severe). This is not a limitation of the analysis approach itself but rather a limitation of the paradigm of conducting clinical studies excluding patients with advanced degrees of organ impairment. In addition, the assessment of the Child–Pugh score in phase II and phase III studies is challenging, as it needs additional expertise to conduct the assessment. Recent regulatory guidances on diversity and inclusion in oncology clinical trials encouraged sponsors to take a risk-based approach to allow for the enrollment of patients with advanced degrees of organ impairment in clinical trials. As these recommendations are slowly adopted in clinical practice, the implementation of popPK approaches to evaluate the effect of organ impairment will be of increasing importance.[29] popPK modeling has been a useful tool in determining dosing adjustment, or lack thereof, as covered earlier in this tutorial. One example is isavuconazole, administered as the prodrug isavuconazole sulfate, which is indicated for the treatment of invasive aspergillosis and mucormycosis. A popPK model was developed with the combined data from two studies to evaluate isavuconazole PK in HI patients following oral and intravenous single dose.[30] The first study conducted had PK assessed in subjects with HI caused by alcoholic cirrhosis while the other study obtained PK data from the subjects with mild and moderate HI caused by hepatitis B and/or C.[31,32] Simulations of mean concentration–time profiles to steady state showed less than a 2-fold increase in mean trough concentrations for subjects with mild and moderate HI compared with healthy subjects. Furthermore, after administration of the single dose, safety data for subjects with mild and moderate HI were generally comparable to those for healthy subjects in both studies. Given there was a <2-fold increase in trough concentrations and the established safety margin, dose adjustment was deemed to be unnecessary in subjects with mild or moderate HI. An evaluation of available oncology drug approvals by the FDA from 1999 to 2019 identified a popPK "success rate" (meaning where popPK was applied successfully for dosing recommendations in HI) across New Drug Applications and Biologics License

Applications to be 96% and 100%, and 21% and 50%, and 0% and 25% for mild, moderate, and severe HI patients, respectively. This review also discusses the use of categorical covariates versus individual laboratory values as HI assessment in the popPK analysis.[16]

Exposure–response analysis

Understanding the relationship between drug exposure and response (both efficacy and safety) is critical for identifying the optimal dose to maximize the clinical benefit and minimize the safety risk. The efficacious range and the acceptable safety margins are used to guide dosing recommendations in special populations or conditions (e.g., to balance the drug–drug interaction effect of concomitant medications, and in patients with renal and/or HI).

For drugs with a steep exposure–safety relationship and/or extensive hepatic metabolism, an HI study is highly warranted in the early stages of clinical development (just after proof-of-concept has been reached) to guide dose recommendation across varying degrees of HI during later stages of development and to avoid excluding patients with advanced degrees of HI from phase II/III studies.

The proposed labeled dose needs to provide an efficacious/therapeutic range of exposures with an acceptable safety profile to the target population. It should account for the exposure differences in this subpopulation such that the expected exposure range is within the defined efficacious/safe range. It is important to mention that due to the limited number of patients with different degrees of HI enrolled in dedicated HI studies, the exposure–response relationship is typically determined in the entire population, predominantly those with normal hepatic function. However, additional factors need to be considered including the safety profile of the drug (e.g., if the drug itself is hepatotoxic), the higher frequency of QTc prolongation in patients with chronic liver diseases,[33] as well as formulation limitations, and so on.

PBPK modeling to predict drug PK changes in HI

PBPK modeling is a useful tool to predict PK changes that are associated with different levels of HI. This modeling technique combines patient-specific factors (such as physiology, anatomy, biochemistry, genetics, and disease conditions) with drug-specific factors (such as protein binding, permeability, metabolism, and transport) to enable the prediction of PK parameters of the drug, using specific study designs and algorithms. Impactful changes in these patient- or drug-specific factors or the study design can be quantified by the PK parameters predicted. Several pathophysiological and biochemical changes occur in patients with progressive HI, making this technique very useful in the prediction of the impact of the physiological changes on drug PK during disease progression. The general principles and concepts applicable to PBPK modeling techniques as well as best practice guidelines are well described in the literature[34–38] and will not be discussed here.

PBPK models are designed to simulate various changes that occur in the body during hepatic cirrhosis and its progression, which are likely to impact the absorption, distribution, metabolism, transport, and excretion of drugs.[39,40] Robust mechanistic PBPK models for a population with different levels of HI (Child–Pugh scores mild, moderate, and severe) account for these changes observed during hepatic disease progression, to enable optimal prediction of the changes in PK. These changes are further influenced by demographic characteristics such as age, sex, body mass, comorbidities, and ethnicity. Some of the key physiological and biochemical changes for modeling consideration includes a reduction in the functional liver mass and volume,[22–24] changes in drug metabolizing enzyme expression and activities,[22,26–27] increase in cardiac output,[28,29] changes in transporter function,[30,31] reductions in hematocrit,[22] decrease in plasma protein binding,[32,33] changes in renal function,[34,35] and gastrointestinal changes.[27,36,37]

The quantitative changes used in generating virtual populations representing Child–Pugh mild, moderate, and severe, respectively, within a commercially available population-based simulator, have been published elsewhere.[39]

Simulations using PBPK modeling can be useful in designing clinical studies (especially with regard to the drug dosing and duration considerations) that are intended to determine the impact of different degrees of HI on drug PK and dosage. PBPK simulations can also be used to supplement limited data when recruitment is difficult. As an example, the PK of a single dose of eliglustat (a drug used in Gaucher disease type 1) in HI was determined in a phase I study. This was followed by PBPK modeling and simulation to predict the PK changes with multiple dosing and when eliglustat was co-administered with a CYP2D6 or CYP3A4 inhibitor, which led to determining the dose recommendation used for labeling.[41] In another example, clinical trials showed lower clearance of isavuconazole (an antifungal drug) in patients with mild and moderate HI, but data in patients with severe HI were not available. PBPK modeling was used to predict the PK in this group and to propose dose optimization in these patients.[42] A final example is the case where a PBPK model of alectinib (an

anaplastic lymphoma kinase inhibitor) predicted a ~2-fold increase in alectinib exposure in subjects with moderate and severe HI. These PBPK predictions supported the selection of the reduced alectinib 300 mg dose and the use of extended PK sampling in the clinical study.[43]

The predictive performances of PBPK modeling of 29 compounds were recently determined using observed data from 56 clinical study arms with different degrees of HI.[5] These authors reported that >70% of the area under the plasma concentration–time curve (AUC) ratio predictions were within 2-fold of the observed data. Overestimations of the ratios were seen in some predictions in moderate and severe HI. This suggests that additional data may be required for PBPK modeling to enable model refinement and improvement of model performance in more severe forms of HI.

The limitations of currently available PBPK models for HI were recently reviewed.[44] These authors reported an overestimation of drug exposure with increasing levels of hepatic dysfunction for some drugs. A primary cause of the overprediction has been attributed to the use of the Child–Pugh scoring systems in current PBPK models. In addition, some PBPK models did not account for changes in specific drug parameters. A further challenge is the availability of reliable clinical data in HI for model construction.

CHALLENGES AND OPPORTUNITIES

It is noteworthy that currently available PK reports in HI patients are solely based on the PK data emerging from hepatic diseases such as alcoholic liver disease, hepatitis B and C, and less common diseases such as acute hepatitis D or E, primary biliary cirrhosis, primary sclerosing cholangitis, and alpha-1 antitrypsin deficiency. This can be seen as the first and foremost limitation that the results obtained from the PK studies conducted in HI patients with the aforementioned liver diseases more often drive the dosing recommendations disproportionately for drugs in the larger subset of HI population. The impact of severe HI, such as hepatic encephalopathy and end-stage liver disease, on the PK/PD of drugs remain unknown. Therefore, in the coming years increasing efforts to understand the impact of severe HI on drug PK and PD are warranted. This knowledge may result in improved drug dosing, thereby optimizing the therapeutic benefits and patient care by maintaining the pharmacological therapeutic window for drugs in patients with varying degrees of HI.

Furthermore, there is an existing discordance in the ways of assessing liver dysfunction as well as classifying/staging liver disease severity. The US FDA recommends the use of the Child–Pugh score for classifying liver impairment in PK studies in subjects with HI.[9] A potential caveat is that the score was not originally intended to guide dose modification in patients with HI. In fact, it was developed to guide operative mortality in patients undergoing hepatic resection and remained unmodified for five decades since its inception. That said, the Child–Pugh system has several limitations including the need for clinical evaluations (i.e., ascites and encephalopathy) which might not be readily conducted during routine evaluations, especially for most oncology indications. A review of FDA-approved oncology compounds showed prevalent use of Child–Pugh classification for dedicated HI studies in non-cancer subjects while NCI classification is commonly used in cancer patient studies.[15] This may reflect more prevalent real-world use of NCI classification in oncology settings. Furthermore, dedicated HI studies typically exclude patients with advanced degrees of ascites and encephalopathy. Additionally, ascites and encephalopathy are typically medically and therapeutically managed. Thus, the assessment of these clinical features might reflect their status under management and will not reflect the true degree of hepatic dysfunction. That said, there are limitations of using NCI classification as well. As with Child–Pugh, NCI classification was not validated to evaluate extent of drug exposure changes with different HI categories. Finally, the NCI system tends to classify subjects as less hepatically impaired than Child–Pugh. Therefore, enrollment of subjects who are classified as NCI 'severe' impaired is considered an operational challenge.[15] Despite the aforementioned limitations, if Child–Pugh classification is used it must be assured that the subjects included in the study have an adequate range of decrease in serum albumin and increase in serum bilirubin and PT.[10,45,46] Alternatively, non-traditional approaches must be implemented utilizing both exogenous markers as well as endogenous biomarkers coupled with Child–Pugh classification system for more accurate staging of liver diseases. Recently, endogenous biomarkers have been applied to evaluate alteration in CYP3A activity in vivo.[47–50] Shin et al.[51] demonstrated the utility of the urinary 11β-hydroxytestosterone (11β-OHT)/testosterone concentration ratio and plasma 4β-hydroxycholesterol (4β-OHC) concentration as CYP3A endogenous markers. For instance, one alternative approach is the assessment of impaired metabolic capacity for the subject to be studied and assessing the alteration in drug PK, particularly if the investigational drug is a CYP3A4 probe drug/substrate. For instance, a recent oncology study reported the use of endogenous markers to evaluate CYP3A enzyme activity in non-small cell lung cancer (NSCLC) patients receiving a standard cisplatin regimen with antiemetics, including aprepitant,[52] which is a substrate of CYP3A4 that inhibits and induces CYP3A4 enzyme activity.[53] This study utilized the urinary 11β-OHT/testosterone concentration ratio and

plasma 4β-OHC concentrations as CYP3A endogenous markers to quantitatively evaluate the time course of CYP3A metabolic activity in NSCLC patients.[52] Similarly, some exogenous markers are increasingly employed to assess the hepatic drug elimination mechanism such as antipyrine, MEGX (monoethylglycinexylidide, a lidocaine metabolite),[45] indocyanine green (ICG),[46] and galactose.[10] Efforts should be made to guide parallel use of these markers along with Child–Pugh classification for assessing the liver function (i.e., assessment of CYP3A activity and hepatic drug elimination) and thereby leading to more accurate staging of liver disease. In the coming years, we expect to see increasing efforts in the pursuit of developing higher concordance around the use of hepatic function assessment methods as well as staging liver disease severity in clinical practices.

CONCLUSIONS

The PK of many xenobiotics is substantially altered in patients with hepatic diseases for which the liver is the primary metabolizing organ. HI can impact the drug PK via diminishing the activity of drug-metabolizing enzymes, reducing the hepatic blood flow, altering the protein binding levels of drugs, or reducing the levels of plasma protein by interfering with its synthesis. The extent of these PK-based alterations is contingent on various drug-related characteristics such as whether the drug has low or high hepatic extraction as well as the severity of the liver disease. Liver diseases generally lead to alterations in PK but may sometimes cause changes in drug PD. Collectively, these alterations in drug PK/PD ultimately guide the need for dosing adjustment in patients with HI. The regulatory agencies have issued guidances providing the rational basis for the need and design for conducting PK studies in patients with varying degrees of HI. The results from the PK studies conducted in HI patients drive the dosing recommendations for drugs in this population. The FDA recommends evaluating the PK of drugs in subjects with HI if hepatic metabolism constitutes more than 20% of their elimination or if they have a narrow therapeutic range.[9] These guidance documents provide insights into the design and conduct of PK studies in HI patients as well as laying out a good framework with regard to the data analysis approaches for sponsors/investigators. That said, the conduct of full clinical PK trials in HI patients may not always be necessary and sometimes not feasible at all. In such cases, modeling and simulation strategies may be utilized to support regulatory approval. As described in the section on the application of modeling and simulation tools to assess impact of HI on drug PK, there are a myriad of literature examples supporting the utilization of in silico tools including but not limited to popPK, PBPK modeling, and exposure–response analysis in lieu of conducting PK studies in HI patients. These modeling and simulation tools have been applied to assess the need for dosing adjustment or lack thereof in patients with HI (an example is discussed under the popPK part of the section on the application of modeling and simulation tools), although limitations of currently available PBPK models for HI still exist[44] and additional data may be required for PBPK modeling to enable model refinement and improvement of model performance. Regardless of the approach utilized, the results generated will be translated into safe and efficacious dose recommendation in the label for HI patients.

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CONFLICT OF INTEREST

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