Analysis of US Food and Drug Administration Oncology Approvals on the Characterization of Hepatic Impairment Effect and Dosing Recommendations

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Patients with cancer and advanced hepatic impairment (HI) (i.e., moderate and severe impairment) are often excluded from first-in-patient, phase II, and phase III studies. Thus, dose recommendations for this subgroup of patients are often derived using a combination of dedicated phase I studies conducted in participants without cancer and a population pharmacokinetic (PK) modeling approach. A standardized risk-based approach to guide the evaluation of HI in patients with cancer is needed. In this review, we evaluated available oncology drug approvals by the US Food and Drug Administration (FDA) from 1999 to 2019, identified strategies utilized by sponsors to characterize the effect of HI on the PK of oncology drugs, and assessed regulatory expectations for each strategy. Finally, we constructed a decision tree that complements current FDA guidance to enable efficient evaluation of the effect of HI on PK and provide guidance for dose recommendations.

Chronic liver disease (CLD) accounts for ~ 2 million deaths per year worldwide, and its prevalence has been steadily rising.[1,2] Different etiologies including chronic hepatitis B or C, alcohol-related liver disease, and nonfatty liver disease can lead to CLD.[2] Hepatic metastasis and anticancer drug–induced toxicities are the common cause of CLD in patients with cancer, while fibroproliferative disease (e.g., cirrhosis) is the major contributor to hepatic insufficiency in patients without cancer (e.g., hepatitis) and in hepatocellular carcinoma.[3–5]

Because liver remains the primary site for drug metabolism and/or biliary excretion of small molecules, liver dysfunction can affect drug pharmacokinetics (PK) through reduced metabolic capacity, reduced blood flow, changes in protein binding, and/or altered transporter expression.[6] Cytochrome P450 (CYP) enzyme activities have been shown to be significantly reduced in liver disease.[7] Importantly, these changes appear to be etiology dependent where reduction of CYP3A activity has been shown in fatty liver disease.[8] Given the complex underlying etiologies, understanding the effect of HI on drug disposition and the magnitude of change in PK are important for providing appropriate dose recommendations for patients with liver insufficiency.

Patients with cancer and advanced degrees of HI are often excluded from first-in-human, registrational phase II/III studies;[9] therefore, dose recommendations for these subpopulations are informed through dedicated HI clinical studies conducted typically as single-dose studies in otherwise healthy participants. Results from HI studies are assessed in the context of exposure–response relationships to derive dose recommendations.

The US Food and Drug Administration's (FDA's) guidance recommended that sponsors conduct dedicated HI studies when the hepatic metabolism and/or excretion is > 20% of the elimination of the parent drug or active metabolite; for drugs with a narrow therapeutic index; or for drugs with unknown metabolism.[10] These dedicated studies are conducted in either "full" or "reduced" design. A full design includes all degrees of HI, while a reduced study design assesses one or two but not all levels of HI categories. The results of the reduced study design may guide whether studying the missing categories is needed. Additionally, hepatic dysfunction can also be assessed as a covariate in population PK modeling.

This review aimed to propose a decision tree to guide the evaluation of HI in relationship to PK changes based on current regulatory guidance and industry practices over the years. To guide this objective, we reviewed oncology approvals by the FDA to identify successful strategies in informing dosing recommendations for patients with liver insufficiency.

METHOD

FDA oncology approvals between 1999 and August 2019 were reviewed, focusing on strategies used at the time of new drug application (NDA) and biologicals license application (BLA) to assess the impact of HI on oncology drug exposure and inform dose recommendation in HI patients. Cell therapies, vaccines, and cancer-supportive therapies (e.g., treatments of chemotherapy-associated cytopenia or bisphosphonates) were excluded. The evaluation included FDA review documents (e.g., clinical pharmacology and biopharmaceutics reviews, multidiscipline reviews), initial US prescribing information, and approval letters in addition to information from *clinicaltrials.gov* and published literatures.

HI assessment strategies were classified into six categories as presented in **Table S1**. The two major criteria considered were (i) whether a dedicated HI study was conducted and if conducted, what its design was (full vs. reduced) and (ii) whether population PK approach was used to assess

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the effect of HI using data collected from clinical trials in different stages of drug development.

Dedicated HI studies conducted were evaluated for study design and sample size. Additional information was considered, including elimination route, PK linearity vs. nonlinearity, study design (single vs. multiple dose and sample size), study population (participants without cancer vs. patients with cancer), classification systems (National Cancer Institute classification (NCIc) vs. Child-Pugh classification), and exposure–response relationships. Adequacy of the proposed study design was assessed via FDA review documents, labeling recommendations, and postmarketing requirements (PMRs) / postmarketing commitments (PMCs).

The review of the population PK approach focused on (i) molecule type (small vs. large), (ii) number of participants included for each HI category, and (iii) interindividual variability on drug clearance (CL). The population PK approach was considered "successful" when a dosing recommendation was provided in a specific category or the label stated that HI categories or liver function biomarkers had no effect on drug exposure. Cautionary language was not considered "successful" given unclear clinical guidance.

GENERAL FINDINGS

Overview of HI characterization strategies

A total of 165 FDA oncology initial approvals were identified, and 117 oncology approvals are in the scope of this review (87 and 30 for small and large molecules, respectively) (**Figure 1**). The breakdown of oncology approvals included in the analysis by HI characterization strategy, small vs. large molecules, and PMRs/PMCs is presented in **Table 1**. Overall, no clear trend was observed between the HI characterization strategy and the type of molecule.

Most small molecules 68% (59/87) were submitted either with results from completed or ongoing HI studies (**Table 1**). NDAs that included full dedicated HI studies (Strategy 1A and 1B) did not receive PMRs/PMCs related to HI. For NDAs that included reduced HI studies (Strategy 2A and 2B), 81% (25/31) were directly accepted for labeling recommendations without PMRs/PMCs. However, there were six approvals (acalabrutinib, abiraterone acetate, dacomitinib, everolimus, enzalutamide, and pexidartinib) where additional studies were warranted. The potential rationales for the PMRs/PMCs are provided in **Table S2**.

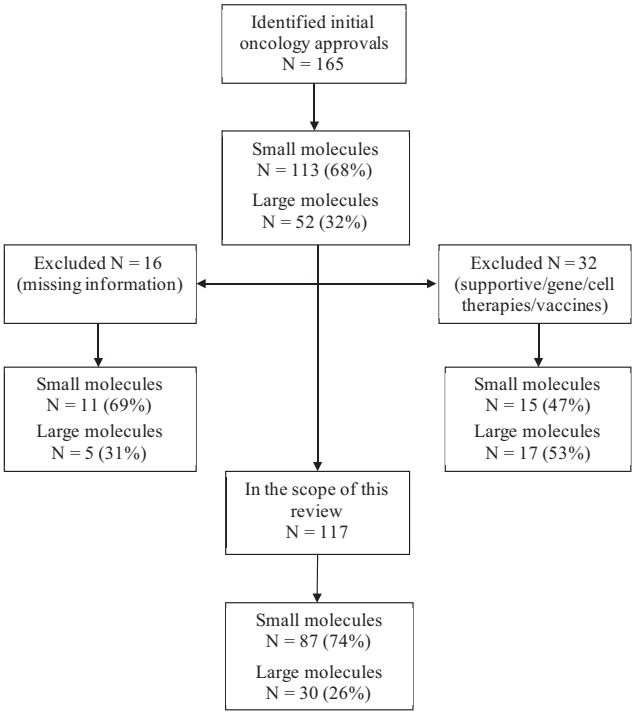

Figure 1 Flow Diagram of included FDA (US Food and Drug Administration) oncology approvals between 1999 and 2019. Analyzed large molecules included monoclonal antibodies (n = 23), ADCs (antibody drug conjugates) (n = 5), and fusion proteins (n = 2).

In NDAs that were submitted without dedicated studies (Strategy 3 and 4), 81% (13/16) and 67% (8/12) received PMRs/PMCs related to HI for Strategy 3 and 4, respectively (**Table 1**). NDAs that did not receive PMRs/PMCs were bendamustine, pralatrexate, and pemetrexed sodium (Strategy 3 population PK only) and omacetaxine mepesuccinate, lenalidomide, lutetium Lu 177 dotatate, and nelarabine (Strategy 4, no population PK and dedicated studies) (further discussed below). Subgroup safety analyses for these compounds were not conducted or not presented in FDA review documents.

Except for brentuximab vedotin, none of the reviewed BLAs conducted dedicated HI studies (i.e., utilized either Strategy 3 or 4) (**Table 1**). Only two BLAs (9%, 2/23), bevacizumab and daratumumab received PMRs/PMCs to conduct additional HI assessment, and both submissions used Strategy 3 (further discussed below).

Dedicated HI Studies (Strategy 1A, 1B, 2A, and 2B)

Small molecules. A total of 82 studies for 80 compounds (2 studies were conducted for each of gefitinib and sorafenib) with available information on study design were identified (**Figure 2**). Most compounds with linear PK were evaluated in single-dose studies (59/66, 89%), while multiple-dose studies were conducted or planned for arsenic trioxide, gefitinib, imatinib, sorafenib, talazoparib, trametinib, and vemurafenib (11%, 7/66) despite PK linearity (**Figure 2**). All multiple-dose studies for these seven compounds were conducted or planned in patients with cancer. Interestingly, for drugs with nonlinear PK (n = 16), single-dose studies were conducted or planned for 8/16, 50% of these agents (afatinib, ceritinib, dabrafenib, idelalisib, ivosidenib, neratinib, olaparib, and ribociclib) (**Figure 2**). All single-dose studies were conducted or planned in patients without cancer except for olaparib.

A total of 71 dedicated HI studies with available information on sample size were identified. The median number of participants included in these dedicated HI studies was 9 (range: 4–25), 8 (range 4–39), 8 (3–20), and 7 (1–32) for normal, mild, moderate, and severe HI subgroups, respectively (**Table 2**). The relationship between observed exposure changes from the dedicated studies and magnitude of the proposed dose reduction is presented in **Figure 3**. The line of unity in **Figure 3** depicted the dose adjustment required to produce equivalent exposures in patients with different HI degrees to those with normal hepatic function. For example, a twofold area under the concentration-time curve (AUC) increase for a drug in patients with moderate HI may necessitate a 50% dose reduction from the standard dose in this population. Dose adjustments were in general inversely proportional to observed changes in PK around the line of unity. Most deviations may be attributed to the specific therapeutic

Table 1 Summary of hepatic impairment submission strategies

	Hepatic Impairment (HI) Characterization Strategy (*N* = 117)					
Strategy	**1A**	**1B**	**2A**	**2B**	**3**	**4**
Dedicated HI study approach	Full		Reduced		Not conducted	
Population PK approach	Yes	No	Yes	No	Yes	No
Small molecules (*n* = 87) *n* (%)	24 (28)	4 (5)	23 (26)	8 (9)	16 (18)	12 (14)
Postmarketing requirements/commitments *n* (%)[a]	—	—	5 (22)	1 (13)	13 (81)	8 (67)
Large molecules (*n* = 30) *n* (%)	—	—	1 (3)[b]	—	23 (77)	6 (20)
Post marketing requirements/commitments *n* (%) [a]	—	—	—	—	2 (9)[c]	—
Total *n* (%)[d]	24 (21)	4 (3)	24 (21)	8 (7)	39 (33)	18 (15)

Summary of hepatic impairment submission strategies in initial oncology approval and postmarketing requirements or commitments.
PK, pharmacokinetic; PMCs, postmarketing commitments; PMRs, postmarketing requirements; —, not applicable.
[a]Reported percentage was calculated as the number of compounds that received PMRs/PMCs relative to the total number of compounds in each strategy. PMRs/PMCs that were issued requesting the sponsor to submit results from ongoing studies without a change in study design were not considered.
[b]Dedicated study was conducted for brentuximab vedotin. We considered this study to be reduced design given that the inclusion criteria were to only include Child-Pugh A and B. One patient with severe (Child-Pugh C) HI was included due to exception.
[c]Bevacizumab and daratumumab both received PMRs requesting additional safety data and clinical PK analysis for patients with HI.
[d]Percentage is calculated using total review oncology approvals, *N* = 117.

window for each compound (e.g., exposure–safety and efficacy relationships) and/or limitations or restrictions in dosage form (**Figure 3**). However, there were cases where dose adjustment deviates significantly from the line of unity (i.e., large underadjustment or overadjustment).

Large molecules. Assessment of the effect of hepatic dysfunction on the PK of biologics was not routinely conducted via dedicated HI studies as only one BLA with a dedicated study (brentuximab vedotin) was identified (**Table 1**).[11] Brentuximab vedotin is an antibody drug conjugate (ADC) that is linked to hepatically cleared small molecule payload, monomethyl auristatin E.[12] Brentuximab vedotin was evaluated in a dedicated HI study with reduced design (**Table 2**). Dedicated HI studies were not conducted for the other four identified ADCs (inotuzumab ozogamicin, gemtuzumab ozogamicin, moxetumomab pasudotox, and polatuzumab vedotin).

Population PK Approach (*Strategy* 1A, 2A, and 3)

Small molecules. Most NDAs included population PK modeling that assessed HI as either continuous (liver function biomarkers) or categorical covariates (mild, moderate, and severe) (*N* = 63/87, 72%), sum of Strategy 1A, 2A, and 3). Of those NDAs that used Strategy 3 (population PK approach

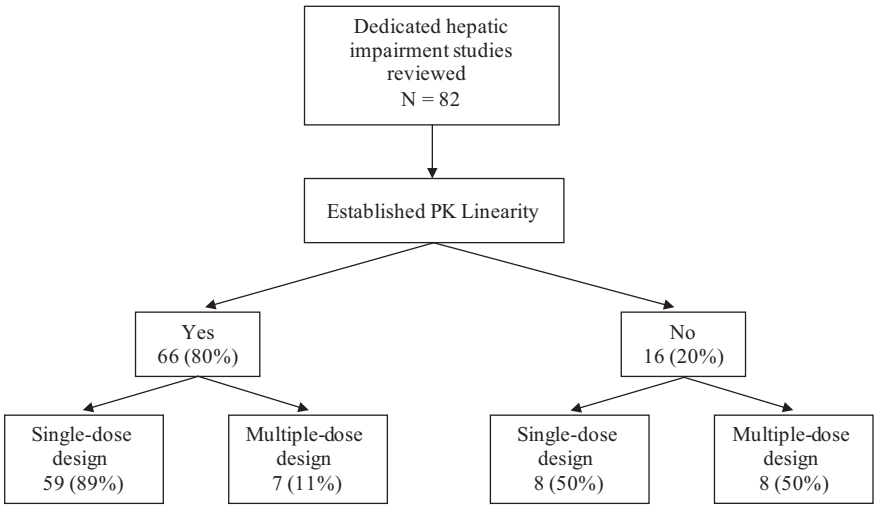

Figure 2 HI study design by PK linearity. Study design refers to PK evaluation portion of the study. A total of 80 compounds were included (two studies were conducted for each of gefitinib and sorafenib). HI, hepatic impairment; PK, pharmacokinetic.

Table 2 Number of participants included in the dedicated HI studies

	Small molecules		Large molecules[a]	
HI categories	Median (min–max)	Number of studies	Median (min–max)	Number of studies
Normal	9 (4–25)	71	8 (8–8)	1
Mild	8 (4–39)	57	1 (1–1)	1
Moderate	8 (3–20)	70	5 (5–5)	1
Severe	7 (1–32)	47	1 (1–1)	1

HI, hepatic impairment.
[a]Brentuximab vedotin. Dedicated study was conducted for brentuximab vedotin.

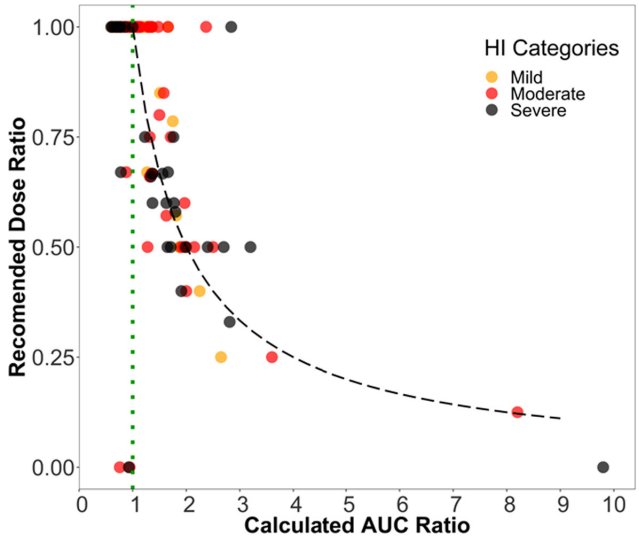

Figure 3 Dose adjustment relative to changes in exposure. Ratios were calculated as recommended dose or AUC in HI/normal hepatic function (N_{drug} = 56). The dashed line depicts the recommended dose adjustment required to produce equivalent exposures in patients with normal hepatic function. For example, a twofold increase in PK exposure would lead to 50% dose reduction. The vertical dotted line marks the AUC ratio of 1 which indicates similar exposure between participants with HI and participants with normal hepatic function. Gefitinib and brentuximab were removed from the data presentation. Brentuximab combined HI categories into one category of impaired hepatic function. Two studies were conducted for gefitinib (one in HI due to cirrhosis and one in HI due to liver metastases), and clear guidance on dose adjustment was not provided. Dose normalized exposure differences from dose-escalation studies were not included. AUC, area under the concentration-time curve; HI, hepatic impairment; PK, pharmacokinetic.

only, n = 16), 13 (81%) received PMRs or PMCs to study the impact of HI subgroups that were limited or not included in the population PK analyses, especially in cases where HI was assessed as continuous variables (**Table 1**). The three approvals (19%, 3/16) that did not receive PMRs/PMCs were for bendamustine hydrochloride, pralatrexate, and pemetrexed sodium (further discussed below) (**Table 1**).

Collectively, a total of 34 NDAs with only population PK analysis were identified (**Table 3**). In general, none of the population PK analyses that assessed HI as continuous variables (21%, 7/34) resulted in "successful" labeling recommendations (**Table 3**). Population PK analyses that evaluated HI as categorical covariate and included sufficient numbers of patients resulted in a dosing recommendation for the corresponding HI category. This includes 25 cases for mild HI with a median number of participants of 49 (range 15–118) and 3 cases for moderate HI with a median number of participants of 17 (range 7–27) (**Table 3**). Population PK analyses that were not "successful" in supporting a dose recommendation for the moderate or severe category were those that included ≤ 4 participants in each subgroup, i.e., 11 cases in moderate HI and all cases (n = 7) in severe HI categories (**Table 3**). The initial labeling for bendamustine was not considered "successful" as the initial US Prescribing Information cautioned against the drug use in patients with mild HI, which was not considered to be a clinically actionable recommendation.[13]

Large molecules. A total of 24 BLAs that utilized a population PK approach to assess an HI effect on PK were identified (**Table S3**). There were 67% (16/24) and 33% (8/24) population PK analyses that assessed HI as a categorical and continuous covariate, respectively (**Table S3**). A similar trend was observed compared with small molecules: BLAs with population PK analyses that evaluated HI as a categorical covariate were more "successful" at supporting a dosing recommendation (**Table S3**). Population PK analyses for avelumab, ziv-aflibercept, mogamulizumab-kpkc, and tagraxofusp-erzs all included five or fewer participants in the moderate HI categories and resulted in "successful" labeling recommendation despite a wide range of interindividual variability in CL that ranged from 25.4 to 126% (**Table S3**).

INTERPRETATION AND PRACTICAL IMPLICATIONS OF KEY FINDINGS

To our knowledge, this represents the first review to evaluate FDA oncology approvals and propose a decision tree for characterization of an HI effect on exposure (**Figure 4**). This article complements the current FDA and European Medicines Agency (EMA) guidances and recent thinking on the topic with an industry perspective into efficient characterization specifically for oncology compounds.[10,14,15] Evaluation of an HI effect on exposure generally followed the FDA guidance, yet further standardization of the evaluation strategies is still needed to expedite development and avoid unnecessary PMRs/PMCs.

Several factors need to be considered for the choice of full vs. reduced design. None of the NDAs that included full dedicated studies received PMRs/PMCs. Full design is preferred in several scenarios, such as if exposure differences were observed in the mild

Table 3 Number of participants included in population PK analyses to support USPI labeling for small-molecule oncology drugs

Small molecules (n = 34)[a]	Continuous variables[b] (n = 7, 21%)	Categorical variables[b] (n = 27, 79%)			
Hepatic function measurement	**Liver function tests (n = 7)**	**Normal (n = 27)**	**Mild (n = 26)**	**Moderate (n = 14)**	**Severe (n = 7)**
"Successful" labeling (n)	0	NA (reference)	25 (96%)	3 (21%)	0 (0%)
Number of participants median (min–max)	NA	285[c] (52–611)	49 (15–118)	17 (7–27)	NA
IIV on CL or CL/F (% CV) median (min–max)	NA	NA (reference)	40.7 (15.7–67.0)	40.7 (31.9–50.5)	NA
"Failed" labeling (n)	7 (100%)	NA (reference)	1[d] (4%)	11 (79%)	7 (100%)
Number of participants median (min–max)	250 (154–596)	NA (reference)	26 (26–26)	2 (1–4)	1 (1–3)
IIV on CL or CL/F (% CV) median (min–max)	37.0 (19.3–76.6)	NA (reference)	33.3	45.6 (26.9–64.0)	43.0 (26.9–64.0)

% CV, percent coefficient of variation; CL, clearance; CL/F, apparent clearance; HI, hepatic impairment; IIV, interindividual variability; NA, not applicable, PK, pharmacokinetic, USPI, US Prescribing Information.
[a]Population PK analyses from Strategy 3 and Strategy 1A/2A when results from dedicated studies were not available at the time of submission. [b]The effect of HI was evaluated in population PK analysis as continuous variables (aspartate aminotransferase (AST), alanine aminotransferase (ALT), and/or total bilirubin (TBI)) or categorical variables (mild, moderate, severe, or hepatically impaired as National Cancer Institute classification (NCIc)) during covariate analysis. [c]Summary statistics for normal HI categories were reported for n = 25. [d]Bendamustine USPI cautioned its use in patients with mild HI in the initial labeling.

group (via a population PK approach), a steep exposure–safety relationship, or wide-scale use in the target population with different degrees of HI is expected. However, such a design might not always be needed as reduced-design HI studies were sufficient in most cases to derive labeling recommendations in the evaluated groups without PMRs/PMCs. Few compounds with reduced-design studies were issued PMRs/PMCs to supplement knowledge in the unstudied categories, mainly the severe group. This could be due to (i) exposure differences observed in the mild and moderate vs. normal groups, (ii) safety considerations including exposure–safety relationship, and (iii) the expected wide-scale use in the target population (e.g., abiraterone acetate and enzalutamide used for treatment of prostate cancer generally diagnosed in older patients who might have HI) (**Table S2**). Despite pexidartinib conducting a reduced-design HI study that included a moderate group using Child-Pugh classification, the FDA requested a dedicated study in patients with moderate HI using NCIc as there was an insufficient number of participants in the moderate NCIc after reclassification from Child-Pugh classification.[16] Child-Pugh classification and NCIc (or similar approaches[17–19]) have been used over the years. A prior publication by our group discussed the potential impact of the discordance between these two classification systems on PK assessment of oncology drugs. The pexidartinib example further highlights regulatory interest in evaluating this discordance. Our article showed that Child-Pugh classification was used for all dedicated HI studies conducted in participants without cancer while NCIc was used for the majority of dedicated studies or population PK analyses conducted in patients with cancer (except for liver cancers which used Child-Pugh).[20] We also showed that NCIc tends to classify participants as less hepatically impaired compared with Child-Pugh classification.[20]

Most Strategy 3 and 4 submissions (i.e., no dedicated studies) were issued PMRs/PMCs (**Table 1**); however, few examples did not. This could be due to the unknown metabolic profile at the time of submission (omacetaxine mepesuccinate, bendamustine, and pralatrexate) or predominant renal or extrahepatic elimination pathway (lenalidomide, lutetium Lu 177 dotatate, pemetrexed, and nelarabine).[21–29] Though PMRs/PMCs were not issued for drugs with an unknown metabolic profile, the FDA indicated that assessment of HI may be needed pending results from mass balance studies, which were issued as PMRs.[21–23] Strategy 4 (no dedicated studies, no population PK) is not recommended even if an impact of HI on exposure is unlikely; for these compounds, sparse PK sample collection and population PK analyses should be planned.

Dedicated HI studies were more commonly conducted for small molecules where liver metabolism is the predominant clearance pathway, while large molecule elimination is primarily driven via nonspecific proteolytic degradation and/or target-mediated disposition. The only BLA that included a dedicated HI study was brentuximab vedotin that has a hepatically eliminated small molecule payload. Dedicated HI studies were not conducted for other identified ADCs. Polatuzumab vedotin had the same payload as brentuximab vedotin and its label incorporated experience with monomethyl auristatin E from brentuximab vedotin (i.e., avoid use for patients with moderate or severe HI). This highlights the potential for cross-learning across ADC programs with common payload to inform dosing recommendation. Only two BLAs required additional HI assessment (bevacizumab and daratumumab). For bevacizumab, the sponsor was requested to assess PK in a rodent model of hepatic dysfunction and evaluate clinical PK data that included patients with HI.[30] For daratumumab (anti-CD38 antibody), the sponsor was requested to

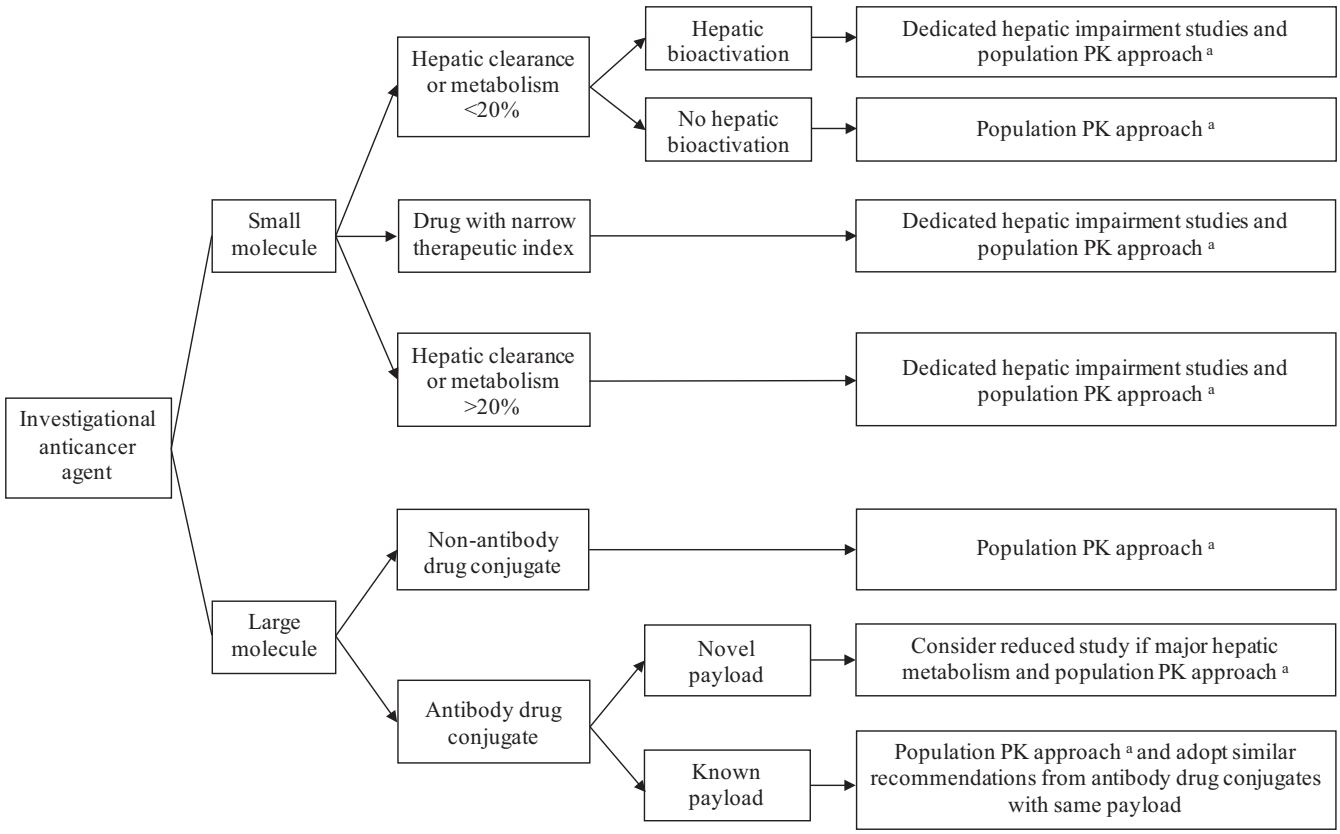

Figure 4 Decision tree for characterizing the effect of HI on the investigational oncology agent. A population PK approach refers to conducting population PK analysis by including patients with cancer with HI from phase I, II, and III trials (HI evaluated as categorical variable during covariate analysis). HI, hepatic impairment; PK, pharmacokinetic.

collect additional safety data in patients with baseline HI from ongoing clinical trials due to increased rates of grade ≥ 3 adverse events (AEs), treatment discontinuation and death due to AEs in baseline mild HI patients.[31,32] Another potential reason is the CD38-mediated Ca^{2+} signaling in hepatocytes and infiltration of inflammatory cells expressing mitochondrial proteins (including CD38), which may be involved in the pathogenesis of primary biliary cirrhosis.[32–34]

Multiple-dose studies conducted in patients with cancer are considerably more expensive and lengthier to conduct compared with single-dose studies in participants without cancer. The decision for single vs. multiple-dose study design should be driven by PK properties. For compounds with linear PK, a single-dose PK study design is sufficient given that steady-state results can be extrapolated. For molecules with nonlinear PK, results from a single-dose may underestimate the impact of HI on exposure after multiple dosing, thus multiple-dose studies are preferred. Multiple-dose studies may also be conducted if the compound cannot be administered to participants without cancer due to lack of adequate safety margin. In which case, the study is conducted in patients with cancer where a washout to evaluate PK might not be feasible in this population. We highlighted seven compounds that exhibited PK linearity yet the sponsors conducted or planned multiple-dose studies in patients with cancer (**Figure 2**), likely because of the safety margin of these agents (mostly narrow safety margin compounds or chemotherapeutic agents). For drugs with long half-lives and/or those that can only be given to patients with cancer, multiple-dose study design is typically utilized.

The rationale behind single-dose studies for compounds that exhibited nonlinear PK (n = 8) remains unclear. Of these, all single-dose studies were conducted or planned in patients without cancer except for olaparib. The dose proportionality for olaparib could not be concluded based on available PK data which were inconsistent across individual trials.[35] The dedicated HI study for olaparib was conducted in patients with cancer and consisted of a single-dose PK assessment portion followed by safety evaluation.[36] This design may be justified by the relatively short half-life (14.9 hours) for olaparib, which may allow a washout in patients with cancer without concerns regarding the duration of treatment interruption.[37]

The median number of participants included in different HI groups for dedicated studies was consistent with the recommendation from the FDA guidance (six or more). Yet, some HI subgroups included more patients (e.g., up to 39 in the mild HI subgroup) (**Table 2**). These studies with more patients were typically designed as dose escalation studies to determine the maximum tolerated dose or recommended phase II dose in each subgroup (e.g., pazopanib and temsirolimus).[38,39]

Dedicated HI study results were often interpreted in the context of safety evaluation to derive dose recommendation that would provide exposure ranges within the no-effect boundary established for each compound. Most dose adjustments were inversely

proportional to the observed changes in exposure (e.g., a recommendation of 50% dose reduction from standard dose with an ~ twofold AUC increase). Exceptions to this rule were observed which may be attributed to the specific therapeutic window for each compound and/or limitations in dosage form (**Figure 3**). For example, if exposure is associated with increased AEs in the hepatically impaired patients or this subgroup of patients are known to be more vulnerable to known AEs of this drug (e.g., QTc prolongation), a more conservative recommendation may be followed either via a higher than proportional dose reduction or a recommendation to avoid use in this subpopulation (e.g., ponatinib and vandetanib recommended to avoid use in certain HI groups despite generally similar exposure to participants with normal hepatic function).[40–42]

Our review showed that a population PK approach is successful in characterizing exposure differences and providing dosing recommendations in lieu of dedicated studies when an adequate number of participants were included for each category; the limited ability to derive dose recommendation in advanced HI categories was due to inadequate sample size rather than a limitation of the approach itself. Population PK "success" rates across NDAs and BLAs were 96% and 100%, 21% and 50%, and 0% and 25% for mild, moderate, and severe groups, respectively (**Table 3 and Table S3**). The rationale for the initial bendamustine label, which cautioned against the drug use in patients with mild HI, is unclear because the analysis included a reasonable number of participants in the mild HI category ($n = 26$) and showed no meaningful effect of mild HI on bendamustine exposure (**Table 3**)[13] Population PK analyses that failed to provide a dose recommendation for moderate or severe HI groups all included six or fewer participants, although there were cases (mostly for large molecules) where a labeling recommendation was derived based on a very limited number of participants. The ≥ 6 number is also consistent with the FDA recommendation for dedicated studies. As recent recommendations to broaden clinical trial eligibility to include patients with advanced HI are implemented, population PK modeling can be a very useful approach to derive dose recommendation in lieu of dedicated studies.[9,43,44]

Ideally, HI should be assessed as categorical covariates rather than individual lab values in the population PK analyses since HI categories provide the grouping basis for dose adjustment and are defined by commonly used classification systems. Use of a classification system was more successful and informative at supporting labeling recommendation. Additionally, the quality of the population PK analyses and interindividual variability on CL may also impact sample size. For a drug with an intrinsically low interindividual CL variability, a smaller sample size might be acceptable compared with a drug with an intrinsically high CL variability, where a much larger sample size might be needed.[45]

Safety considerations may necessitate dedicated studies even when a population PK approach was sufficient at supporting a labeling recommendation. For example, the population PK analysis for venetoclax (mild $n = 69$, moderate $n = 7$) and the proposed dose monitoring and ramp-up period were accepted by the FDA for labeling recommendations.[46] However, a dedicated HI study was still warranted due to increased AEs in the moderate group and small sample size ($N = 5$) based on the subgroup safety analysis.[47]

The utility of physiologically-based pharmacokinetic (PBPK) modeling in predicting the effect of organ impairment on exposure is evolving. A systematic review by the IQ Consortium showed that PBPK predictions were within twofold of the observed data in participants with HI in ~ 75% of the compounds evaluated ($n = 56$).[48] The exposure differences in the moderate and severe groups tended to be overpredicted, which could be due to the lack of clear understanding of all pathophysiological changes during liver cirrhosis and the association between these changes and the degree of HI. PBPK predictions of ibrutinib initially overestimated exposure in participants with hepatic impairment. However, evolving understanding of the impact of pathophysiological changes associated with HI and incorporation of these changes in the model allowed for improved predictions of ibrutinib exposure in different HI subgroups.[49]

In some cases, validated PBPK models for compounds with nonlinear PK were used to predict exposure changes in participants with HI.[50] A PBPK model reasonably predicted exposure changes of simeprevir, a drug with nonlinear PK, in hepatitis C virus–infected participants with mild hepatic impairment.[51] Therefore, there is growing evidence that validated PBPK models might be used to supplement clinical data (e.g., for single-dose HI studies for compounds with nonlinear PK to assess HI impact at steady state) if nonlinearity can be accurately and reasonably incorporated in the model. Additionally, PBPK could be used to provide knowledge in the unstudied HI categories for studies using a reduced design and importantly for guiding the design of dedicated studies. Mechanistic understanding of the impact of HI on drug-metabolizing enzymes, biliary transport, perfusion, protein binding, and other pathophysiological changes should be incorporated in PBPK models.

Based on the regulatory guidance for evaluation of HI, our discussion from this review, and our understanding of the metabolic and elimination pathways, a decision tree is proposed to facilitate efficient characterization of the effect of HI on the investigational agent's exposure (**Figure 4**).

We acknowledge that only FDA oncology approvals were evaluated and submissions that failed approval were not available. Our review was limited by publicly available FDA review documents, which might be missing data due to proprietary information. Assumptions were made during the data collection period, such as that population PK analyses were assumed to not be conducted if such analysis was not included or discussed in the FDA review documents.

In summary, regulatory guidances from the FDA and the EMA on the topic represent the main framework for informing strategies for characterizing the effects of HI on exposure. Our review complements the regulatory guidances and provides an industry perspective into the most efficient strategies to characterize HI effect on exposure with emphasis on oncology compounds. While we reviewed previous approvals to develop a decision tree for future compounds, two important quickly evolving aspects that may impact approaches to characterizing HI on exposure were highlighted. First, broadening the clinical trial eligibility criteria of phase II/III studies would allow more patients with advanced degrees of HI. Coupled with our findings on the success

of utilizing sparse sampling from phase II/III studies via population PK approach in lieu of dedicated studies in providing dosing recommendations for the evaluated groups, this approach could play a more prominent role in the future. Second, PBPK may also play an important role with further understanding of pathophysiological changes with HI and their correlation to exposure differences.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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