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Clinical Significance of Transient Asymptomatic Elevations in Aminotransferase (TAEAT) in Oncology

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Abstract: Monitoring for liver injury remains an important aspect of drug safety assessment, including for oncotherapeutics. When present, drug-induced liver injury may limit the use or result in the discontinuation of these agents. Drug-induced liver injury can exhibit with a wide spectrum of clinical and biochemical manifestations, ranging from transient asymptomatic elevations in aminotransferases (TAEAT) to acute liver failure. Numerous oncotherapeutics have been associated with TAEAT, with published reports indicating a phenomenon in which patients may be asymptomatic without overt liver injury despite the presence of grade ≥ 3 aminotransferase elevations. In this review, we discuss the occurrence of TAEAT in the context of oncology clinical trials and clinical practice, as well as the clinical relevance of this phenomenon as an adverse event in response to oncotherapeutics and the related cellular and molecular mechanisms that may underlie its occurrence. We also identify several gaps in knowledge relevant to the diagnosis and the management of TAEAT in patients receiving oncotherapeutics, and identify areas warranting further study to enable the future development of consensus guidelines to support clinical decision-making.

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Hundreds of drugs are associated with drug-induced liver injury (DILI),[1,2] which has a wide spectrum of clinical and biochemical manifestations, ranging from transient asymptomatic elevations in aminotransferases (TAEAT) to acute liver failure.[1,3] Most cases ($>90\%$) of DILI resolve fully within several weeks after drug discontinuation, although some cases can persist as chronic low-level enzyme elevations for 6 to 12 months despite the drug cessation.[4,5] Drug adaptation may also occur, defined as the phenomenon whereby an agent fails to cause progressive worsening of DILI beyond what are generally transient, low-level, asymptomatic reversible alanine aminotransferase (ALT) elevations despite the drug continuation.[6]

Although international working groups have defined threshold levels of ALT or aspartate aminotransferase (AST) to distinguish acute DILI from mild elevations,[7,8] the clinical significance of higher level (ie, grade 3 [G3] and grade 4 [G4]) asymptomatic transient elevations has not been extensively studied,[9] especially in oncology.[10] In addition, there are gaps in the understanding of mechanisms leading to significantly elevated aminotransferase levels, specifically in cases of asymptomatic and transient presentations without clinical signs of hepatocyte damage.

Herein, TAEAT is used to indicate the occurrence of transient asymptomatic G3 and G4 elevations in aminotransferases (ALT and/or AST) without associated elevations in bilirubin or alkaline phosphatase or corresponding histologic liver abnormalities. A review of TAEAT in oncology clinical trials and clinical practice is provided. In addition, the gaps in our current understanding of the phenomenon are identified, including those areas where consensus guidelines and practical suggestions for clinicians involved in managing oncology patients with elevated aminotransferases may offer value.

TAEAT DEFINITION

The Common Terminology Criteria for Adverse Events version 5 grades AST and ALT levels[11] based on reference to upper limits of normal (ULN) or baseline values (if baseline is abnormal). G1 elevations are $>1.0–\leq 3.0\times$ULN (1.5–3.0×baseline), and G2 elevations are $>3.0–5.0\times$ULN/baseline, both of which are below the threshold defining acute DILI.[7] Only G3 ($>5.0–20.0\times$ULN/$>5.0–20.0\times$baseline) and G4 ($>20\times$ULN/($>20\times$baseline) elevations meet currently accepted criteria for acute DILI.[7,8] Although all AST and ALT elevations require close monitoring to establish whether they are isolated and transient events and to evaluate the risk of continuing drug therapy, the heightened significance of TAEAT requires further investigation.

Just as a third clinical phenotype has been proposed for DILI (ie, indirect hepatotoxicity),[12] TAEAT might be best classified as a fourth DILI phenotype (ie, part of an extended spectrum of drug adaptation). This distinguishes TAEAT from clinically overt hepatotoxicity, given that after initial aminotransferase elevations develop in patients with TAEAT, levels gradually decline over days to weeks. Thus, TAEAT are akin to the adaptive response seen among several other drug classes; notably the statins[6] and tacrine, which has reached G4 ALT elevations.[13]

TAEAT does not always preclude continuation of the causative oncotherapeutic agent and may resolve quickly without treatment interruption, as shown for blinatumomab, tyrosine kinase inhibitors, interleukin (IL)–2, interferon-α, and fluorouracil.[14,15] However, regulatory restrictions and treatment guidelines that recommend (or mandate) treatment interruption/discontinuation for asymptomatic ≥G3 AST and ALT elevations can limit data generation for further identification and characterization of TAEAT.[16] Additional research is needed to establish criteria for isolated ≥G3 AST and ALT elevations, so clinicians can differentiate between those that spontaneously resolve without consequences (ie, TAEAT) and those that may progress further to liver-related symptoms such as jaundice or acute or subacute hepatic failure, that is, coagulopathy (international normalized ratio [INR] ≥1.5) and new onset encephalopathy.[17,18]

Elevated Aminotransferases and Risk of Liver Injury

Zimmerman[1] observed that drug-induced hepatocellular jaundice potentially predicted serious and even fatal outcomes. Subsequently, "Hy law" was coined and defined as serum ALT levels >3×ULN combined with total bilirubin levels >2×ULN, after the exclusion of other underlying causes to help identify patients most likely to progress to serious liver injury.[19] Elevated ALT levels are sensitive for liver injury and, although not entirely specific, are viewed as being more predictive than AST levels. Healthy liver tissue has excess bilirubin-excreting capacity; therefore, hepatic injury sufficient to cause hyperbilirubinemia (ie, 2×ULN) represents a degree of hepatocyte loss that may become irreversible.[18,20,21]

Hy law criteria have been historically useful for predicting serious drug-induced hepatocellular liver injury, with ~1 in 10 Hy law cases leading to death from liver-related causes or the need for liver transplant.[1,4,6,18,22] Failure to detect a Hy law case in clinical trials does not imply an acceptable hepatocellular safety profile because large clinical trials (>3000 patients) are needed for a high probability of detection, trial sizes that are rare in oncology. However, the detection of ≥2 Hy law cases in clinical trials is a strong predictor of significant risk and may prevent further development.[18]

Even when Hy law cases are detected during clinical evaluation, the risk:benefit to the population must be considered before determining whether clinical trials should continue.[10,23] In oncology, some degree of hepatotoxicity may be acceptable given the potential benefit provided.[10] The US Food and Drug Administration's (FDA) general recommendations for evaluating and monitoring symptomatic DILI in clinical trials suggest that modification for special patient populations (eg, oncology) may be needed, particularly for those with underlying hepatic involvement.[10,18] Recent approvals of oncotherapeutics demonstrate that a certain degree of hepatotoxicity, with careful monitoring of hepatic function, is acceptable to bring novel potentially life-prolonging drugs to market (Table 1). For instance, the risk of hepatotoxicity among all new drug classes was highest for oncotherapeutic agents approved by the FDA in recent years.[37]

TAEAT IN ONCOLOGY

Monitoring for liver injury during discovery, clinical development, and postapproval phases of the drug life cycle remains essential.[6] However, one third of 500 oncotherapeutic trials failed to clearly define thresholds for abnormal liver injury.[38] In addition, the 2009 FDA guidance for the evaluation and management of potential hepatotoxicity[18] did not specifically address risk:benefit considerations, nor did it specifically consider the phenomenon of TAEAT. Considering the risk:benefit of drugs is particularly important for patients with potentially fatal malignancies who may be prescribed agents with known adverse side effects including hepatotoxicity,[10,39,40] which may otherwise preclude their use in more benign conditions. Assuming therapeutic benefits are sufficient, further data and guidance would help support the clinical community and health authorities if some instances of DILI (including TAEAT) are to be accepted.

Incidence of TAEAT

The frequency of TAEAT for tumorocentric drugs approved since 2018 is summarized in Table 2. The percentages of patients with ≥G3 aminotransferase elevations ranged from 1% to 15% for ALT and 0% to 15% for AST.

Cancer immunotherapy (eg, immune checkpoint inhibitors [ICI] and bispecific T-cell engager molecules) is now standard for various solid and hematological cancers.[68–70] Immuno-oncology (IO) is expanding rapidly, with multiple ICIs, immune agonists, T-cell engagers, and cellular therapies under investigation. ICI-induced aminotransferase elevations have typically been G2–G3[71–74]; however, deaths due to hepatic failure have been rarely reported.[71,75] The frequency of TAEATs for IO drugs approved since 2018 is summarized in Table 2, and those without the mention of hepatic abnormalities are summarized in Table 3.

Dose-Limiting Toxicities and TAEAT

The determination of dose-limiting toxicities (DLTs) is crucial in establishing the maximum tolerated dose and recommended dose for phases 2 and 3.[82] Current FDA guidance recommends consideration be given to discontinuing an investigational drug in an asymptomatic patient if ALT or AST levels are >8×ULN or >5×ULN for >2 weeks.[18] In patients with any symptoms of hepatitis or with total bilirubin levels >2×ULN or an INR >1.5, drug discontinuation is recommended when AST or ALT levels are >3×ULN.[18] Consensus guidelines have been developed for assessing and managing suspected symptomatic DILI in clinical trials in patients with underlying liver disease.[83,84] In otherwise asymptomatic patients with ALT elevations at baseline, ALT elevations ≥5×baseline (or absolute values ≥300 U/L) are the current threshold for interrupting treatment. However, current FDA guidance does not specifically address the occurrence of TAEAT, which takes on greater importance when evaluating oncotherapeutic agents for life-threatening malignant diseases.

TAEAT does not appear to preclude further clinical development, with several approved clinical trials defining G3 aminotransferase levels as DLTs only when levels remain elevated for ≥7 days (eg, ClinicalTrials.gov: NCT03439280) or are associated with symptomatic disease (eg, ClinicalTrials.gov: NCT03918278). Interestingly, matching a current DLT definition, a median TAEAT duration of 7 days has been demonstrated in a real-world study in cancer patients treated with ICI, although the maximal duration of TAEAT was 128 days.[85] On the basis of this and given risk:benefit assessment in cancer patients, a question is raised as to whether the further extension of acceptable TAEAT duration during clinical studies in

TABLE 1. Oncology Therapies Approved by the FDA Since 2018 With Hepatotoxicity Warnings in the Product Label

Drug (Ref)	Drug Class/Therapeutic Use	Warning	Liver Chemistry Elevations	Dose Modifications
Tumorocentric drugs				
Selpercatinib[24]	Kinase inhibitor/various solid tumors	Hepatotoxicity: monitor ALT and AST before starting the therapy and Q2W for first 3 mo, then monthly	Serious hepatic AE in 2.6% ALT increased: G3–4, 9% AST increased: G3–4, 8% Bilirubin increased: G3–4, 2%	G3–G4 AST or ALT: withhold doses until G1 or baseline Reduce dose by 2 dose levels and monitor ALT/AST weekly Increase by 1 dose level after a minimum of 2 wk
Capmatinib[25]	Kinase inhibitor/metastatic NSCLC	Hepatotoxicity: monitor liver chemistry before starting therapy and Q2W for 3 mo, then monthly	ALT increased: G3–4, 8% AST increased: G3–4, 4.9%	G3 AST or ALT without increase in bilirubin: withhold doses until recovery to baseline ALT/AST G4: permanently discontinue Hy law criteria: permanently discontinue
Tucatinib[26]	Kinase inhibitor/HER2+ breast cancer	Severe hepatotoxicity (G3–4, 9.2%); monitor ALT, AST, bilirubin before starting therapy and Q3W	ALT increased: ≥G3, 8% AST increased: ≥G3, 6% Bilirubin increased: ≥G3, 1.5%	G3 AST/ALT or G3 bilirubin: withhold until recovery to G1 or baseline levels; resume at next lower dose level G4 AST/ALT or G4 bilirubin: permanently discontinue Hy law criteria: permanently discontinue
Entrectinib[27]	Kinase inhibitor/NSCLC, solid tumors	Hepatotoxicity: monitor ALT, AST Q2W during first month and then monthly	ALT increased: G3–4, 2.9% AST increased: G3–4, 2.7%	G3–4 AST/ALT: withhold until recovery to G1 or baseline, resume at same dose if G3 event resolved within 4 wk, or a reduced dose for recurrent G3 events or G4 event Recurrent G4 AST/ALT: permanently discontinue Hy law criteria: permanently discontinue
Pexidartinib[28]	Kinase inhibitor/TGCT	Boxed warning: can cause serious and potentially fatal liver injury, available only through a restricted program	ALT increased: ≥G3, 20% AST increased: ≥G3, 12% ALP increased: ≥G3, 4.9% Bilirubin increased: ≥G3, 3.3%	ALT/AST ≥3–5×ULN: withhold and monitor weekly, if ≤3×ULN within 4 wk, resume at reduced dose; otherwise, permanently discontinue ALT/AST >5–10×ULN: withhold and monitor twice weekly, if ≤3×ULN within 4 wk, resume at reduced dose; otherwise, permanently discontinue ALT/AST >10×ULN, permanently discontinue (continue to monitor)

Polatuzumab vedotin-piiq[29]	CD79b-directed antibody-drug conjugate/relapsed or refractory diffuse large B-cell lymphoma	Hepatotoxicity; monitor liver enzymes and bilirubin	G3 and G4 transaminase elevations developed in 1.9% and 1.9%, respectively; laboratory values suggestive of DILI occurred in 2.3% of patients	Bilirubin > ULN to ≤ 1.5×ULN or AST > ULN; no starting dose adjustments required when administering polatuzumab vedotin to patients with mild hepatic impairment (bilirubin > ULN to ≤ 1.5×ULN or AST > ULN).
Tagraxofusp-erzs[30]	CD123-directed cytotoxin/BPDCN	Hepatotoxicity: monitor liver enzymes and bilirubin	ALT increased: ≥ G3, 30% AST increased: ≥ G3, 37% ALP increased: ≥ G3, 1% Bilirubin increased: ≥ G3, 0%	ALT or AST increase > 5×ULN; withhold treatment until transaminase elevations are ≤ 2.5×ULN
Calaspargase pegol –mknl[31]	Asparagine-specific enzyme	Hepatotoxicity: monitor for toxicity through recovery from cycle	Transaminases increased, ≥ G3, 52% Bilirubin increased, ≥ 3G, 20%	Total bilirubin > 3×ULN to no more than 10×ULN; withhold treatment until total bilirubin levels go down to ≤ 1.5×ULN Total bilirubin > 10×ULN; discontinue and do not make up for missed doses
Larotrectinib[32]	Kinase inhibitor/solid tumors with an *NTRK* gene fusion without a resistance mutation, that are metastatic without the option of surgical resection, with no satisfactory alternative treatments	Hepatotoxicity: monitor liver test results, including ALT and AST Q2W during the first month of treatment, then monthly and as clinically indicated	ALT increased: G3–4, 3% AST increased: G3–4, 3% ALP increased: G3–4, 3%	Withhold and modify dosage, or permanently discontinue based on severity Reduce the starting dose by 50% in patients with moderate (Child-Pugh B) to severe (Child-Pugh C) hepatic impairment
Duvelisib[33]	Kinase inhibitor/relapsed or refractory CLL or SLL, relapsed or refractory follicular lymphoma	Hepatotoxicity: monitor hepatic function	ALT or AST increase > 3×ULN and total bilirubin > 2×ULN, 2% Patients with B-cell malignancies ALT increased: ≥ G3, 8% AST increased: ≥ G3, 6% ALP increased: ≥ G3, 2% Patients with CLL/SLL ALT increased: ≥ G3, 7% AST increased: ≥ G3, 3% ALP increased: ≥ G3, 0%	G2 ALT/AST elevation (3–5×ULN): maintain dose and monitor at least weekly until return to <3×ULN G3 ALT/AST elevation (> 20×ULN): withhold and monitor at least weekly until return to <3×ULN; resume treatment at same dose (first occurrence) or at reduced dose for subsequent occurrence G4 ALT/AST elevation (> 20×ULN): discontinue treatment
Binimetinib[34]	Kinase inhibitor in combination with encorafenib/unresectable or metastatic melanoma with *BRAF* V600E or V600K mutations	Hepatotoxicity: monitor liver chemistry before and during treatment and as clinically indicated	In combination with encorafenib ALT increased: G3–4, 6% AST increased: G3–4, 2.6% ALP increased: G3–4, 0.5%	G2 AST or ALT increased: maintain dose; if no improvement within 2 wk, withhold treatment until improved to G0–1 or to pretreatment/baseline levels and then resume at the same dose G3 AST or ALT increased: for first occurrence of G3 (or recurrent G2), withhold treatment for ≤ 4 wk; if levels improve to G0–1 or

TABLE 1. (*continued*)

Drug (Ref)	Drug Class/Therapeutic Use	Warning	Liver Chemistry Elevations	Dose Modifications
				pretreatment/baseline levels, resume at the same dose; if no improvement, discontinue. For recurrent events, consider permanent discontinuation G4 AST or ALT increased: for first occurrence, permanently discontinue or withhold treatment for $\leq$4 wk; if levels improve to G0–1 or pretreatment/baseline levels, resume at the same dose; if no improvement, discontinue; for recurrent events, permanent discontinuation For patients with moderate or severe hepatic impairment, the recommended dosage is 30 mg orally taken BID
Lutetium Lu 177 dotatate[35]	Radiolabeled somatostatin analog/GEP-NET	Hepatotoxicity: monitor transaminases, bilirubin and albumin	ALT increased: G3–4, 4% AST increased: G3–4, 5% ALP increased: G3–4, 5% Bilirubin increased: G3–4, 2%	Bilirubinemia $>$3×ULN, or hypoalbuminemia <30 g/L, with a prothrombin ratio <70%: withhold until complete resolution, resume at reduced dose; for hepatotoxicity requiring treatment delay of $\geq$16 wk, permanent discontinuation
Immuno-Oncology Drugs Cemiplimab-rwlc[36]	PD-1–blocking antibody/metastatic CSCC or locally advanced CSCC not qualified surgery or curative radiation	Evaluate clinical chemistries, including hepatic and thyroid function, at baseline and periodically during treatment	Immune-mediated hepatitis: any grade, 2.1%; G4, 0.2%; G5, 0.2% AST increased: G3–4, 3%	Hepatitis: withhold if AST/ALT increases to $>$3×ULN/baseline to $\leq$10×ULN/baseline or if total bilirubin increases $\leq$3×ULN Discontinue if AST/ALT increases to $>$10×ULN/baseline or total bilirubin increases to $>$3×ULN

ALP indicates alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; BPDCN, blastic plasmacytoid dendric cell neoplasm; CLL, chronic lymphocytic leukemia; CSCC, cutaneous squamous cell carcinoma; DILI, drug-induced liver injury; FDA, US Food and Drug Administration; G, Grade; GEP-NET, gastroenteropancreatic neuroendocrine tumor; NSCLC, non–small cell lung cancer; NTRK, neurotrophic receptor tyrosine kinase; PD-1, programmed death receptor-1; Q2W, every 2 weeks; SCLC, small-cell lung cancer; SLL, small lymphocytic lymphoma; TGCT, tenosynovial giant cell tumor; ULN, upper limit of normal.

TABLE 2. Tumorocentric and Immuno-oncology Therapies Approved by the FDA Since 2018 With Elevated Aminotransferases in the Product Label

Drug (Ref)	Drug Class/Therapeutic Use	Hepatic-Related Event	Notes
First FDA approved in 2020			
Tumorocentric therapies			
Belantamab[41]	B-cell maturation antigen/RRMM	AST increased: G3–4: 2% ALP increased: G3–4: 1%	Patients with mild to moderate renal impairment included in pivotal study
Decitabine/cedazuridine[42]	Nucleoside metabolic inhibitor and cytidine deaminase inhibitor/myelodysplastic syndrome	Transaminase increased: G3–4, 3%	
Pertuzumab/trastuzumab/hyaluronidase zzxf[43]	HER2/neu receptor antagonists + endoglycosidase/ breast cancer	ALT increased: G3–4, 1.6% AST increased: G3–4, 0.8%	
Tazemetostat[44]	EZH2 inhibitor/RR-FL	ALT increased: ≥G3, 3.4% AST increased: ≥G3, 3.5%	
Lurbinectedin[45]	Alkylating drug/metastatic SCLC	ALT increased: ≥G3, 4% AST increased: ≥G3, 2%	
Ripretinib[46]	Kinase inhibitor/GI stromal tumors	ALT increased: ≥G3, 1.2% Increased blood bilirubin: G1 and G2, 22%	
Sacituzumab govitecan-hziy[47]	Trop-2–directed antibody, topoisomerase inhibitor conjugate /triple-negative breast cancer	ALT increased: ≥G3, 2% AST increased: ≥G3, 3%	Not evaluated in patients with moderate to severe hepatic impairment; some patients with brain metastases included in trials
Pemigatinib[48]	Kinase inhibitor/metastatic cholangiocarcinoma	ALT increased: ≥G3, 4.1% AST increased: ≥G3, 6% Bilirubin increased: ≥G3, 6%	
Tucatinib[26]	Kinase inhibitor/HER2+ breast cancer	Warning: severe hepatotoxicity (≥G3, 9.2%); monitor ALT, AST, bilirubin before starting therapy and Q3W ALT increased: ≥G3, 8% AST increased: ≥G3, 6% Bilirubin increased: ≥G3, 1.5%	Patients with brain metastases eligible for clinical trials
Selumetinib[49]	Kinase inhibitor/ NF1 or PN	ALT increased: ≥G3, 4% AST increased: ≥G3, 2%	
Avapritinib[50]	Kinase inhibitor/metastatic GI stromal tumor	ALT increased: ≥G3, 0.5% AST increased: ≥G3, 1.5% Bilirubin increased: ≥G3, 9%	Excluded patients with brain metastases
Immuno-oncology therapies			
Tafasitamab (in combination with lenalidomide)[51]	CD19-directed cytolytic antibody/ RR-DLBCL	AST increased: ≥G3: 0% Albumin decreased: ≥G3; 0% APPT increased: ≥G3: 4.1	
Brexucabtagene autoleucel[52]	CD19-directed immunotherapy/RR-MCL	ALT increased: ≥G3, 15% AST increased: ≥G3, 15%	Patients with brain metastases excluded from pivotal study
First FDA approved in 2019			
Tumorocentric therapies			
Fam-trastuzumab deruxtecan-nxki[53]	HER2-directed antibody drug conjugate/HER2+ breast cancer	ALT increased: ≥G3, 0.9% AST increased: ≥G3, 0.4%	Bone metastases in 31%/brain metastases in 13%
Zanubrutinib[54]	Kinase inhibitor/MCL	ALT increased: ≥G3, 0.9% Bilirubin increased: ≥G3, 0.9%	Hepatic enzymes ≤2.5×ULN
Darolutamide[55]	Androgen receptor inhibitor/CRPC	AST increased: ≥G3, 0.5% Bilirubin increased: ≥G3, 0.1%	
Alpelisib[56]	Kinase inhibitor/ advanced or metastatic breast cancer	ALT increased: G3–4, 3.5%	
Ivosidenib[57]	IDH1 inhibitor/AML	Newly diagnosed AML: ALT increased: ≥G3, 4% AST increased: ≥G3, 4% ALP increased: ≥G3, 0% Relapsed or refractory AML: ALT increased: ≥G3, 1% AST increased: ≥G3, 1% ALP increased: ≥G3, 1% Bilirubin increased: ≥G3, 1%	

TABLE 2. (*continued*)

Drug (Ref)	Drug Class/Therapeutic Use	Hepatic-Related Event	Notes
Erdafitinib[58]	Kinase inhibitor/ locally advanced or metastatic urothelial carcinoma	ALT increased: G3–4, 1% AST increased: G3–4, 0% ALP increased: G3–4, 1%	
Trastuzumab and hyaluronidase-oysk[59]	Trastuzumab: HER2/neu receptor antagonist; hyaluronidase: endoglycosidase/breast cancer	ALT increased: G3–4, 1.7%	
First FDA approved in 2018			
Tumorocentric therapies			
Gliteritinib[60]	Kinase inhibitor/ relapsed or refractory AML	ALT increased: ≥G3, 12% AST increased: ≥G3, 10% ALP increased: ≥G3, 1%	
Glasdegib[61]	Hedgehog pathway inhibitor/newly diagnosed AML	When used in combination with low-dose cytarabine ALT increased: G3–4, 0% AST increased: G3–4, 1% ALP increased: G3–4, 0% Bilirubin increased: G3–4, 4%	Limitation of use: glasdegib has not been studied in patients with comorbidities of severe renal impairment or moderate to severe hepatic impairment
Lorlatinib[62]	Kinase inhibitor/ALK-positive NSCLC	ALT increased: G3–4, 2.1% AST increased: G3–4, 2.1% ALP increased: G3–4, 1.0%	No dose adjustment for mild hepatic impairment; dose not established for moderate to severe hepatic impairment; potential for hepatotoxicity when used with rifampin
Talazoparib[63]	PARP inhibitor/germ line *BRCA*-mutated HER2-negative locally advanced or metastatic breast cancer	ALT increased: G3, 1%; G4, 0% AST increased: G3, 2%; G4, 0% ALP increased: G3, 2%; G4, 0%	Talazoparib has not been studied in patients with moderate or severe hepatic impairment Mild hepatic impairment had no effect on PK
Dacomitinib[64]	Kinase inhibitor/metastatic NSCLC with epidermal growth factor receptor mutations	ALT increased: G3–4, 1.4% AST increased: G3–4, 0.5% ALP increased: G3–4, 0.5% Hyperbilirubinemia: G3–4, 0.5%	Mild or moderate hepatic impairment had no effect on PK
Iobenguane I 131[65]	Radioactive therapeutic agent/ iobenguane scan positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma requiring systemic anticancer therapy	Patients with PPGL: ALT increased: G3–4, 2% AST increased: G3–4, 2% ALP increased: G3–4, 5%	
Encorafenib[66]	Kinase inhibitor in combination with binimetinib/ unresectable or metastatic melanoma with *BRAF* V600E or V600K mutations	In combination with binimetinib: ALT increased: G3–4, 6% AST increased: G3–4, 2.6% ALP increased: G3–4, 0.5%	
Immuno-Oncology Therapies			
Moxetumomab Pasudotox-tdfk[67]	CD22-directed cytotoxin indicated for relapsed or refractory hairy cell leukemia	ALT increased: G3, 3.8% AST increased: G3, 1.3% Bilirubin increased; G3, 1.3%	Mild hepatic impairment had no clinically relevant effect on PK PK in patients with moderate to severe hepatic impairment is unknown

The following groups terms may be used: AST increased, ALT increased, ALP increased, γ-glutamyltransferase increased, hepatic enzyme increased, hepatic function abnormal, hepatoxicity, liver function test increased, and transaminases increased.

ALK indicates anaplastic lymphoma kinase; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AML, acute myeloid leukemia; APPT, activated partial thromboplastin time; AST, aspartate aminotransferase; DLBCL, diffuse large B-cell lymphoma; FDA, US Food and Drug Administration; FL, follicular lymphoma; G, Grade; GI, gastrointestinal; IDH-1, Isocitrate dehydrogenase-1; MCL, mantle cell lymphoma; MM, multiple myeloma; NF1, neurofibromatosis type 1; NSCLC, non–small cell lung cancer; PARP, poly (ADP-ribose) polymerase; PK, pharmacokinetics; PN, plexiform neurofibromas; PPGL, pheochromocytoma and paraganglioma; RR, relapsed or refractory; SCLC, small cell lung cancer.

patients with aggressive types of cancer (eg, acute myeloid leukemia; AML) is feasible to ensure potentially life-preserving treatment is not being unnecessarily withheld. Illustratively, the results from a prospective, phase 1 study of clofarabine with 2 Gy total body irradiation indicated approximately one third of patients with AML or acute lymphoblastic leukemia experienced ≥G3 ALT and AST elevations without any manifestations of hepatotoxicity.[86]

COMPLICATING FACTORS IN TAEAT ASSESSMENT IN ONCOLOGY

Abnormal Baseline Liver Chemistries

In oncology trials, abnormal baseline liver chemistries can be affected by various factors, including prior anticancer therapies, potentially hepatotoxic concomitant medications, alcohol use, liver metastases, and preexisting chronic liver disease[10,18]; nonetheless, patients may remain asymptomatic.[87] Because pre-existing chronic liver disease (eg, nonalcoholic steatohepatitis and viral hepatitis) might be responsible for baseline aminotransferase elevations, the pretreatment screening of liver chemistries is usually undertaken.[84,88] Although patients with G1 aminotransferase elevations are often enrolled in clinical trials, careful assessment of further on-therapy elevations helps clinicians make informed decisions regarding the management of potential hepatotoxicity.[74] Negative tests for hepatitis B virus and hepatitis C virus are usually a part of inclusion criteria in most clinical trials, and patients with affected liver functions are often included in additional post-registrational clinical studies. As outlined in consensus guidelines for clinical trials in patients with underlying liver disease, elevations in aminotransferases based on baseline values are likely to be more meaningful than ULN comparisons,[74,83,84] as reflected in Common Terminology Criteria for Adverse Events version 5.[11] During such studies and in clinical practice, it is advisable to refer patients with elevated aminotransferases for a hepatology consult for intensive follow-up monitoring to enable early initiation or resumption of potentially life-preserving cancer therapy.

In addition, various oncotherapeutics used as standard of care treatment can potentially lead to elevated aminotransferases, including 6-mercaptopurine treatment for solid tumors,[89] doxorubicin for ALL,[90] mitoxantrone for relapsed or primary refractory ALL,[91] and cisplatin for ovarian cancer.[92] Thus, control arms in phase 3 trials may be associated with reversible elevation of aminotransferases consistent with TAEAT (eg, tyrosine kinase inhibitors).[18,93,94] Furthermore, the lack of a control group in most phase 1 oncology trials makes the assessment of elevated liver enzymes challenging in patients with underlying factors associated with aminotransferase elevations. Thus, the causality assessment by independent DILI experts is considered the current gold standard[95] and essential to assess relatedness in TAEAT. Tools such as the objective scoring system (used in the Roussel Uclaf Causality Assessment Method) can be useful but require a certain degree of expertise and are often combined with expert opinion, as used by the US DILI Network.[96,97]

Concomitant Medications

The use of concomitant medications (eg, antibiotics/antimycotics) may complicate the interpretation of abnormal liver chemistries and the relationship between TAEAT and the oncotherapeutic agent.[98–100] Polypharmacy is prevalent among patients with cancer.[101] It is estimated that approximately one third of the US elderly population (2005 to 2006) was prescribed ≥5 concurrent medications.[102] Medications such as statins, antiepileptics (phenytoin, carbamazepine, and valproic acid), antifungals (ketoconazole and itraconazole), antituberculosis drugs (rifampin and isoniazid), cotrimoxazole, and allopurinol may all potentially elevate aminotransferases.[1,3] Azole antifungals, in particular, are frequently used for prolonged periods in patients with hematologic malignancies, and have been implicated in idiosyncratic DILI, with nearly all azoles associated with minor changes in liver chemistries.[103] The LiverTox Bookshelf and other resources provide an up-to-date summary of drugs implicated in DILI,[2,3] and can aid in the differential diagnosis of elevated liver enzymes in patients being treated for malignancies.

Metastases

The effect of hepatic and bone metastases on liver enzymes is variable and confounded by relatively limited and often contrasting findings in the literature. Although alkaline phosphatase may be elevated with space-occupying lesions (eg, liver metastases) or due to extrahepatic biliary obstruction from enlarged lymphadenopathy in the area of the porta hepatis (as in breast cancer),[104] firm incidence data are lacking. Aminotransferase elevations may reflect the infiltration of liver diseases, such as leukemia or lymphoma,[105,106] or liver tests may remain normal. For example, despite having no obvious liver involvement in AML, autopsy reports indicated hepatic infiltration in >75% of patients.[107] In addition, higher rates of elevated aminotransferases (>5×ULN) were reported in patients treated with onapristone with bone (2.4% to 4.8%) or liver (4.0%to 12.0%) metastases compared with those without these metastases (0.0% to 4.3% and 0.0% to 1.6%, respectively).[108] Similarly, aminotransferases were significantly elevated in patients with solid tumors and liver metastasis versus those without metastases.[109–111] In contrast, a pooled analysis of 31 phase 2 and 3 oncology trials found that the incidence of ALT and AST elevations was generally similar in patients with or without liver metastases.[112]

REAL-WORLD EVALUATION AND MANAGEMENT OF TAEAT IN ONCOLOGY

Limited information is available on how practicing oncologists manage TAEAT or what criteria are used to predict whether the elevated aminotransferases will progress to more serious DILI. A recent real-world US evaluation of elevated aminotransferases associated with IO therapies found that isolated ALT and AST elevations of ≥G3 were relatively transient (up to 128 d with median duration ~7 d), with only 5.3% subsequently progressing to elevated bilirubin levels.[85] In this study, oncologists discontinued ICI therapy in 8% of cases, with 92% of patients proceeding with their anticancer treatment. In 37% of cases, ≥G3 aminotransferase elevations were managed with corticosteroids without interruption of ICI therapy, illustrating decision-making based on risk:benefit assessment. Additional real-world studies are needed to assess current trends in TAEAT management in cancer patients treated with non-IO drugs including drug interruptions/discontinuations, use of corticosteroids, and frequency of liver function assessment. An analysis of 1670 patients in 85 phase 1 oncology studies found similar rates of DILI for patients in immune-based versus targeted therapy trials (5.0% vs. 4.9%); DILI resolved in 96% of patients, with no reports of drug-related liver failure,[113] consistent with TAEAT representing drug adaptation. Nevertheless, additional real-world data and prospective clinical trials in specific oncology populations are needed to identify factors

TABLE 3. Oncotherapeutic Agents Approved Since 2018 With No Mention of Hepatic Adverse Events on the Product Label

Drug (Ref)	Drug Class/Therapeutic Use
Tumorocentric drugs	
Enfortumab vedotin-ejfv[76]	Nectin-4–directed antibody-drug conjugate/urothelial cancer
Apalutamide[77]	Androgen receptor inhibitor/prostate cancer
Selinexor[78]	Nuclear export inhibitor/RRMM
Immuno-oncology drugs	
Daratumumab + hyaluronidase[79]	CD38-directed cytolytic antibody + endoglycosidase/MM
Isatuximab-irfc[80]	CD38-directed cytolytic antibody/RRMM
Mogamulizumab-kpkc[81]	CCR4-directed monoclonal antibody/relapsed or refractory mycosis fungoides or Sézary syndrome after ≥1 prior systemic therapy

MM indicates multiple myeloma; RR, relapsed or refractory.

that predict which patients with elevated aminotransferases are likely to progress to more serious liver injury. Additional work is underway to develop best practice guidelines for the assessment of liver chemistries in oncology trials. In particular, consensus is needed regarding the continuation of an oncotherapeutic agent in patients experiencing TAEAT based on individual risk:benefit assessment.

POSSIBLE MECHANISMS OF TAEAT

It is commonly accepted that cell damage with plasma membrane disruption followed by release of cellular contents into the plasma is principally responsible for aminotransferase elevations present in symptomatic DILI.[114] However, the lack of histologic findings (ie, hepatic necrosis) in liver biopsies from some patients with isolated ≥G3 aminotransferase elevations calls into question the potential alternative mechanisms involved in TAEAT.[115] The release of hepatoprotective cytokines is postulated as one of the main reasons why mild ALT elevations fail to progress in patients in whom drug adaptation is seen, such as with statins.[6,116] Dampening the innate immune response to liver injury or other cellular mechanisms that prevent liver injury from crossing the threshold to irreversibility are suggested as the main reasons that most drugs fail to cause serious liver injury.[117] Several of these potential mechanisms are reviewed below and are likely to apply to all-grade aminotransferase elevations. Once established in preclinical settings, human studies might be warranted to assess not only the mechanisms driving TAEAT, but most importantly, optimal mitigation approaches in clinic.

Role of Liver Cells

Approximately 80% of liver cells are parenchymal (hepatocytes), with the nonparenchymal cells comprising endothelial cells (8%), stellate cells (4%), Kupffer cells (4%), and intrahepatic lymphocytes (4%).[118,119] Infiltrating T cells, natural killer (NK)/NK T cells, Kupffer cells, and infiltrating tumor cells may contribute to aminotransferase elevations.[120] Various studies have shown that activated $CD8^+$ T cells might cause inflammation in the liver leading to elevations in aminotransferases.[121–123] Hepatic NK cells can also respond to a local cytokine milieu and contribute to liver injury by a nonantigen-specific TNF-related apoptosis-inducing ligand-mediated pathway.[124–126] Activated Kupffer cells are a major source of inflammatory mediators such as superoxide, nitric oxide, eicosanoids, cytokines, lysosomal, and other proteolytic enzymes that lead to altered hepatic homeostasis,[127] potentially leading to elevated aminotransferases.

Membrane Blebbing

Large plasma membrane blebs, clear and round cytoplasmic protrusions, may form as a physiological response to activating stimuli and are not the sole indicators of extreme cell stress or initiation of death pathways.[128,129] Their formation may be dependent on external calcium, indicating that signaling events initiating the formation may be downstream of the high-affinity IgE receptor/inositol trisphosphate/calcium release–activated channels ($Fc\varepsilon RI/IP_3$/CRAC) pathway for store-operated calcium entry.[129] Alterations in plasma membrane caused by the absence of oxygen have been reported.[130] Under hypoxic conditions, blebs ruptured and released their contents, including aminotransferases, into the circulation resulting in elevated aminotransferases without overt hepatocellular damage.[130]

Hypoxic Hepatitis and Cytokine Release Syndrome

Hypoxic hepatitis, also known as "shock liver," is characterized by massive, rapid, and transient elevations of aminotransferases (AST often >20–100×ULN) due to an imbalance in hepatic oxygen demand and supply.[131] Hypotension is one of the principal causes of hypoxic hepatitis[132] and is also associated with cytokine release syndrome (CRS).[133] Along with oncotherapeutics such as rituximab,[134] obinutuzumab,[135] oxaliplatin,[136] and lenalidomide,[137] CRS has been reported with bispecific T-cell engager molecules, such as blinatumomab,[138] and chimeric antigen receptor T-cell therapies.[139] Cytokine levels have been shown to be modulated by hypoxic hepatitis[140]; thus, CRS-inducing drugs may be associated with elevations in aminotransferases with or without typical hepatic symptoms, in the context of liver chemistry abnormalities.

Increased Expression of ALT and AST

Induction of expression of the genes encoding ALT and AST is another possible mechanism leading to aminotransferase elevations without apparent injury. Fenofibrate has been shown to increase the expression of genes encoding ALT and AST in human hepatoma cell line HepG2 and by binding of peroxisome proliferator-activated receptor α (PPARα) to the peroxisome proliferator-activated receptor response element in the proximal ALT1 promoter resulting in elevated ALT levels.[141,142] Dexamethasone, used for CRS prophylaxis and treatment,[143] has been shown to elevate the levels of aminotransferases via increased transcription of human and rat ALT1 reporter genes and increased the transcription of *GPT1/GOT1* genes.[142,144,145] Increases in ALT and AST (usually G1–G2, but occasionally G3) induced by bardoxlone methyl are thought to be related to the pharmacologic induction of

aminotransferases via nuclear factor erythroid 2–related factor 2 activation rather than any intrinsic form of hepatotoxicity.[146]

Indirect Effect Via Local Microenvironment

Agents that affect the liver through indirect means may also cause elevated aminotransferase levels. Various oncotherapeutics possess a half-life-extending crystallizable fragment (Fc) domain, which could enhance the immune responses, including antibody-dependent cytotoxicity, complement-dependent cytotoxicity, and antibody-dependent cell-mediated phagocytosis.[147,148] Kupffer cells and NK cells express Fc receptors on their surfaces,[149,150] and their stimulation may result in the production of proinflammatory cytokines such as TNF-α, IL-1β, and IL-6.[149–151] Hence, Fc receptor–mediated cell activation by the Fc fragment of various molecules might lead to TAEAT as a consequence of local inflammation.

Macroenzymes

Type 1 macroenzymes include high molecular mass complexes of AST and ALT with immunoglobulins, which aid in protecting aminotransferases from degradation slowing their clearance and leading to increased serum levels.[152,153] Although the role of immunoglobulins, mostly IgG and IgA, in the formation of type 1 complexes is well established, it remains unknown whether protein-based drugs can contribute to AST and ALT macroenzyme formation. Nevertheless, prolonged elevations of aminotransferases due to macroenzymes may be interpreted as TAEAT.[153,154]

CLINICAL SIGNIFICANCE OF TAEAT AND GAPS IN KNOWLEDGE

Although the clinical significance of symptomatic DILI cases or cases with multiple laboratory abnormalities is well established, there is no consensus on how to interpret and manage TAEAT. Several of the gaps in our current knowledge regarding various aspects of TAEAT, which may benefit from further research, are summarized below.

Should Risk:Benefit Assessment be Used to Determine TAEAT Management?

The determination of when to continue treatment and risk: benefit considerations for various types or stages of cancer are areas requiring further research. The interpretation and clinical significance of a single Hy law case or TAEAT in oncology trials can be especially challenging. Modification of Hy law criteria using fold elevations in liver chemistries in patients with baseline abnormalities[155] have been proposed to improve the assessment of possible TAEAT in oncology trials. Although oncotherapeutic agents causing liver enzyme elevations may still gain FDA approval, specific guidelines are needed to differentiate between management approaches based on risk:benefit assessment for each patient, to identify when to monitor liver chemistries and continue treatment, or when to modify, withhold, or discontinue treatment.

Can Hepatic Histology Help in Understanding the Biology of TAEAT?

Aminotransferases are not only released into plasma after hepatocyte death but also because of extrahepatic causes, such as hemolysis and muscle injury.[114,156] Across a range of indications and patient populations, there are reports of TAEAT without associated significant liver injury, for which extrahepatic causes may be responsible.[86,115,157,158] Aminotransferases are also released into the circulation without cell death. A better understanding of the pathophysiology of TAEAT may help identify the optimal approach to clinical management. In many of the cases described, patients with TAEAT continued treatment and aminotransferase levels either plateaued or resolved; features consistent with drug adaptation. In patients in whom aminotransferases remain elevated and noninvasive investigations show no obvious alternative cause, liver biopsy may be recommended.[159] Although hepatic histology cannot completely establish causality to a specific drug,[115] it is useful in helping to differentiate TAEAT from other causes, such as autoimmune hepatitis.[40,160] Defining the histologic pattern of TAEAT injury can provide an indication of severity, enabling the clinician to balance risk:benefit of continuing the suspected causative therapy.[159]

This is specifically important because minor nonspecific changes can be observed in the biopsy results of patients with TAEAT.[161] From available biopsy data, ≥G3 elevations do not routinely imply liver necrosis,[115] indicating that with some therapies, large increases in aminotransferases may occur without significant hepatocyte death. However, aminotransferase elevations, with or without hyperbilirubinemia, have also been associated with histologic liver injury (particularly with ICI therapy),[73,75] and liver cell necrosis typically occurred with aminotransferase elevations associated with hyperbilirubinemia.[73] Hepatic necrosis or apoptosis distinguishes this type of liver injury from TAEAT. Nevertheless, liver biopsy data are limited, and in some malignancies (eg, those associated with thrombocytopenia), histology may be difficult to obtain. Although ultrasound, magnetic resonance imaging (MRI), and computed tomography are noninvasive alternatives, they provide limited information compared with histologic evaluation. Although several exploratory biomarkers for DILI have been proposed,[162] further validation is required in tandem with biopsies undertaken in the context of DILI to support such validation in different clinical scenarios. Therefore, a need for novel technologies and biomarkers is evident to assess liver injury at a cellular and molecular levels.

Should TAEAT Management Include Drug Interruption and Rechallenge?

For some oncotherapeutic agents, treatment interruption may potentially compromise efficacy outcomes. This raises the question of whether the treatment interruption can be avoided in patients with TAEAT with steroid treatment and careful liver chemistry monitoring to ensure that no subsequent hyperbilirubinemia or clinical symptoms of hepatic injury develop.[85] Desensitization rechallenge is controversial, but may be considered when benefits of therapy outweigh risks.[163] Indeed, for some oncotherapeutics (eg, ICI for solid cancers), rechallenge after TAEAT is increasingly being accepted.[40,71,164–170] The decision to resume treatment after the detection of hepatitis/hepatotoxicity is based on individualized risk:benefit assessments,[40,167–170] and these considerations should likely apply to rechallenge after the confirmation of elevated aminotransferase levels. Although current recommendations for rechallenge are outlined in the approved prescribing information (Table 1), further discussion is needed with a goal to generate patient-tailored decision-making algorithms to ensure optimal patient outcomes.

CONCLUSIONS

In both clinical trials and routine clinical practice, physicians generally focus on monitoring higher grades (≥G3) of aminotransferase elevations. Published reports indicate that some patients are asymptomatic without any overt liver injury

despite having ≥G3 aminotransferase elevations, and these elevations do not progress and may resolve while the drug is continued, a phenomenon similar to drug adaptation associated with nononcology agents. As such, prospective studies of rechallenge in patients with no other signs of impaired hepatic function could be considered. The recognition and understanding of TAEAT within oncology is further complicated by the coexistence of chronic liver disease, liver/bone metastases, prior treatments, and concomitant medications. Despite these challenges, the occurrence of TAEAT with oncotherapeutics may be more common than previously appreciated.

A number of mechanisms is likely involved in these transient, asymptomatic elevations of aminotransferase levels. However, it is not clear whether these mechanisms are drug specific, indication specific, or patient specific. Additional studies aimed at elucidating these mechanisms at a cellular and molecular level are needed to better determine the cause of TAEAT, for both oncotherapeutics and other drugs, including in specific populations, such as those with liver metastases.

In conclusion, TAEAT with ≥G3 elevation of aminotransferases is associated with many oncotherapeutic agents. Although usually reported as an adverse event, its clinical implications remain incompletely understood, as progressive liver injury may not develop. Additional research and clinical studies, including real-world data, are needed to gain a better understanding of TAEAT pathophysiology and management. This increased understanding will enable the development of consensus guidelines for the use of drugs associated with TAEAT in patients with cancer, including in those who have exhausted all other treatment options.

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