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Review Article

Epidemiology and Management of Drug-induced Liver Injury: Importance of the Updated RUCAM

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Abstract

Drug-induced liver injury (DILI) is a major cause of acute liver injury, liver failure, and liver transplantation worldwide. In recent years, immune checkpoint inhibitors have become widely used. This has led to an increase in DILI, for which pathophysiology and management methods differ significantly from the past. As the number of cases of acute liver injury and liver transplantation due to DILI is expected to increase, information about a DILI is becoming more valuable. DILI is classified into two types according to its etiology: intrinsic DILI, in which the drug or its metabolites cause liver damage that is dose-dependent and predictable; and idiosyncratic DILI, in which liver damage is also dose-independent but unpredictable. In addition, depending on the course of the disease, chronic DILI or drug-induced autoimmune hepatitis may be present. The number of DILI cases caused by antimicrobial agents is decreasing, whereas that caused by drugs for malignant tumors and health foods is increasing. The Roussel Uclaf Causality Assessment Method is widely used to assess causality in DILI. Liver injury is a type of immune-related adverse event. The pattern of hepatic injury in immune-related adverse events is mostly hepatocellular, but mixed type and bile stasis have also been reported. Sclerosing cholangitis caused by immune checkpoint inhibitors has also been reported as a unique type of injury. Treatment mainly comprises withdrawal of immune checkpoint inhibitors and steroid administration; however, mycophenolate mofetil may be considered if the disease is refractory to steroids.

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Abbreviations: anti-PD-1, anti-programmed death-1; anti-PD-L1, anti-programmed death ligand-1; AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine transaminase; CYP, cytochrome P450; DI-AIH, drug-induced autoimmune hepatitis; DILI, drug-induced liver injury; ICI, immune checkpoint inhibitors; INR, international normalized ratio; irAE, immune-related adverse event; NAPQI, N-acetyl-p-benzoquinone imine; RCT, randomized clinical trials; RUCAM, Roussel Uclaf causality assessment method.

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Introduction

Drug-induced liver injury (DILI) is a leading cause of liver failure and liver transplantation worldwide. In DILI, causality assessment is the key to diagnosis. The Roussel Uclaf Causality Assessment Method (RUCAM) is the most widely used tool for the diagnosis of DILI worldwide, with RUCAM used to assess causality in 81,856 cases of DILI published by the middle of 2020.[1] In recent years, with the widespread use of immune checkpoint inhibitors (ICIs), a new type of DILI has been observed that requires unconventional approaches to treatment. DILI is expected to increase in the future and there is a growing need for knowledge about it. This review presents findings on DILI, including immune-related liver injury.

Viewpoints

Pharmacokinetics and hepatic metabolism

Drugs are absorbed and distributed from the stomach and intestinal tract and transported via the portal vein to the liver, metabolizing them by enzymes in hepatocytes. Drugs that are not metabolized are transported throughout the body in the bloodstream and exert their effects on target organs. Thereafter, the drugs are excreted. Pharmacokinetics is referred to as ADME from the initial letters of four words (absorption, distribution, metabolism, excretion; Fig. 1).[2] In pharmacokinetics, metabolism is important because it not only reduces or enhances a drug's effects but is also involved in adverse effects. In drug metabolism, hepatic metabolism occurs when a drug is mostly metabolized in the liver, resulting in a reduced effect with less than 40% passing through the kidney. Renal excretion occurs when a drug that is not easily metabolized by the liver is excreted by the kidneys in its unchanged form (>60%). Meanwhile, a drug retaining 40–60% of its form despite hepatic metabolism is said to have undergone hepatic/renal excretion.

In drug metabolism, the liver increases the hydrophilicity of the target substance to prevent accumulation in the tissues and facilitates urinary and fecal excretion. Phase I reactions increase hydrophilicity and are responsible for increasing the water solubility of compounds by forming hydroxyl, amino, and carboxyl groups with processes that include oxidation, reduction, and decomposition. Cytochrome P450 (CYP) is involved in the metabolic reactions of approximately 70% of drugs and is the most important enzyme group in drug metabolism.[3,4] In humans, CYPs in the small intestine, where oral drugs first pass, and CYPs in the liver, where they are expressed in large amounts, are important; among these,

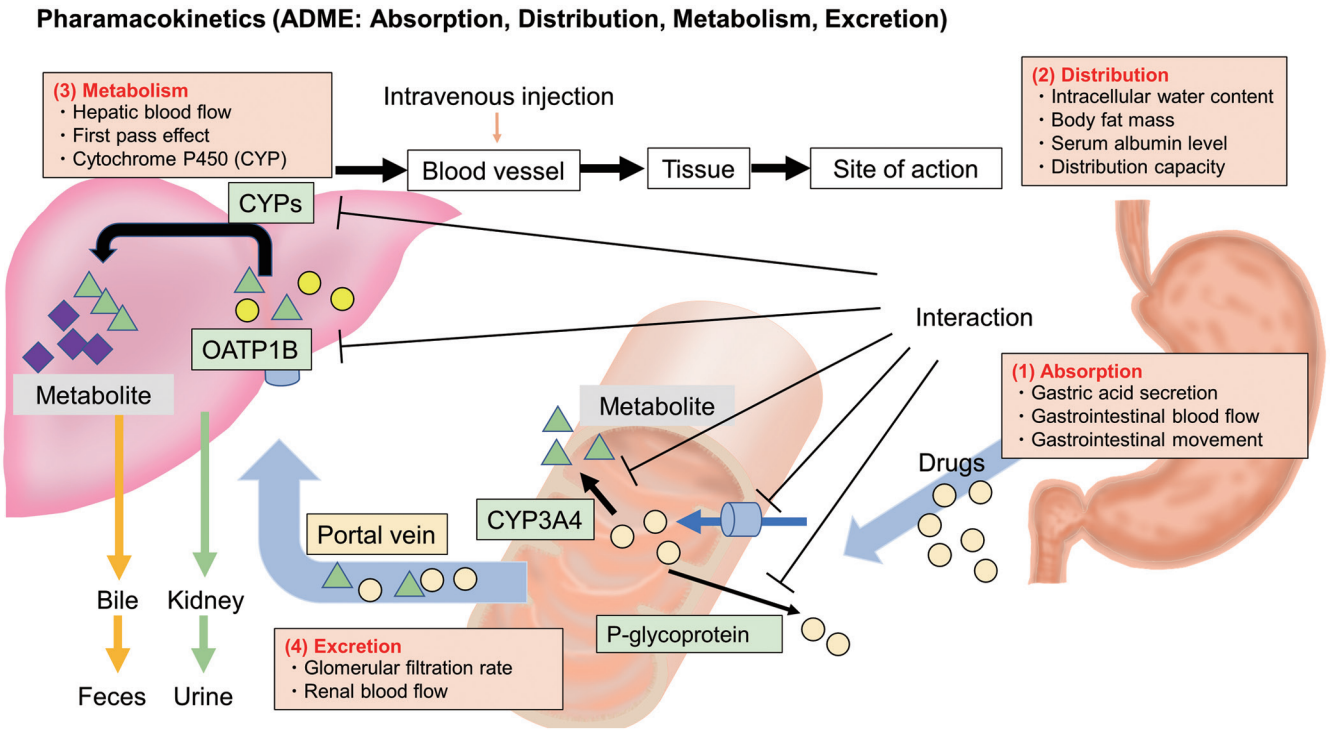

Fig. 1. Pharmacokinetics (ADME: Absorption, Distribution, Metabolism, Excretion).[2] Drugs are absorbed and distributed from the stomach and intestinal tract, transported via the portal vein to the liver and metabolized by hepatic enzymes before excretion. Pharmacokinetics is referred to as ADME from the initial letters of these four words (absorption, distribution, metabolism, and excretion).

CYP3A4 metabolizes several drugs. Phase II reactions include conjugation (sulfuric acid, glucuronic acid, glutathione, acetyl group, and methyl group), further increasing water solubility and facilitating urinary and fecal excretion. Drugs do not necessarily need to undergo a phase I reaction before a phase II reaction, as some drugs directly undergo a phase II reaction.[4]

Drug interactions

When multiple drugs are administered simultaneously, drug effects may be reduced, and adverse effects may occur due to interactions during drug metabolism. Drug-drug interactions are more likely to occur when drugs are metabolized by CYPs due to (1) competitive inhibition, (2) irreversible inhibition (e.g., CYP3A4 with erythromycin), and (3) nonspecific inhibition (e.g., CYP2D6 with cimetidine and CYP3A4 with azole antifungals). For enzymes other than CYP, competitive inhibition in glucuronide conjugation and competitive interaction with organic anion transporting polypeptide 1B (e.g., cyclosporine A and rifampicin) may occur. In other cases, carbapenems may inhibit the hydrolytic enzymes of glucuronide conjugates, resulting in a decrease in the blood concentration of valproic acid when valproate is administered with carbapenems.[5]

Classification of DILI

DILI is classified into two types according to its etiology: intrinsic DILI, in which the drug or its metabolites cause dose-dependent and predictable liver damage; and idiosyncratic DILI, in which the drug causes dose-independent but unpredictable liver damage.[6] Most DILI are idiosyncratic and associated with fever, skin rash, and eosinophilia (allergy). In DILI, adaptation may occur during hepatic injury, which may lessen or disappear even if the patient continues receiving the causative agent. Guidelines of the European Association for the Study of the Liver for treating DILI noted that toxic and idiosyncratic DILI both involve reactive intermediary metabolites that covalently bind to components (proteins) in hepatocytes. It has been pointed out that stress kinases, mitochondrial stress, and endoplasmic reticulum stress are aggravating factors.[6]

Intrinsic DILI

Acetaminophen, an antipyretic analgesic, is the most common causative agent of toxic DILI, accounting for 15–57% of cases of acute liver failure in Western countries.[7,8] Aspirin, amiodarone, chemotherapeutic agents, paraquat (herbicide), carbon tetrachloride, and mushroom poisons may also cause toxic DILI.[8–10] Among these, acetaminophen is the leading cause of acute liver failure in Europe and the USA, with a reported rate of 45.7% in North America and 65.4% in the UK.[11,12] Conversely, DILI caused by acetaminophen is rare in Asia.[13] Acetaminophen in large doses causes hepatocellular toxicity; however, it was reported that hepatotoxicity is not caused by acetaminophen itself but by N-acetyl-p-benzoquinone imine (NAPQI), which is oxidized by CYP2E1. NAPQI is detoxified by glutathione conjugation and excreted in the urine. However, when acetaminophen is taken in large amounts, NAPQI concentration increases and exhausts glutathione reserves. The unmetabolized NAPQI covalently binds to various enzymes and proteins in hepatocytes, resulting in decreased enzyme activity, lipid peroxidation, and liver damage. Liver injury develops rapidly, beginning 8–12 hours after ingestion of high doses of acetaminophen. Generally, acetaminophen intake of ≤1 g per dose does not cause liver damage; ≥5 g results in liver damage, and ≥10 g leads to acute liver failure.[6–8,14] Typically, bilirubin is normal or only slightly elevated, but the plasma aminotransferase activity and the internationally normalized ratio of prothrombin time

Table 1. Clinical features and main causative agents of chronic DILI[8,22,25]

Clinical features of DILI	Causative agents
Fatty liver	5-fluorouracil, diltiazem, cortisone, vitamin A, interferon, NSAIDs, intravenous valproic acid, intravenous tetracycline, tamoxifen, amiodarone, methotrexate, antiretroviral
Nodular regenerative hyperplasia	6-mercaptopurine, azathioprine, vitamin A, platinum, antiretroviral drugs
Hepatocellular adenoma	Anabolic steroids, oral contraceptives
Drug-induced autoimmune hepatitis	Nitrofurantoin, minocycline, hydralazine, methyldopa, interferon, statins, biologics (antibody drugs)
Vanishing bile duct syndrome	Amoxicillin/clavulanic acid, fluoroquinolones, sulfamethoxazole, azithromycin, carbamazepine, lamotrigine, chlorpromazine, allopurinol, demozolomide, ibuprofen
Liver cirrhosis	Amiodarone, methotrexate, vitamin A, valproic acid

DILI, drug-induced liver injury; NSAIDs, nonsteroidal anti-inflammatory drugs.

become very high, peaking at approximately 72 hours.[15] Acetylcysteine can prevent liver injury when administered within 12 hours of acetaminophen overdose, but whether it is effective at later time points is controversial.[16]

Idiosyncratic DILI

Idiosyncratic DILI is classified into allergic or metabolic types. In allergic DILI, the drug or its intermediate metabolites become haptens that bind to proteins in hepatocytes and acquire antigenicity, triggering an immune response that leads to hepatocyte destruction. Fever, skin rash, and eosinophilia often occur, and onset is usually 5 to 90 days after taking the causative drug.[17–19] It is difficult to predict the onset of idiosyncratic DILI because it depends on the patient's genetic condition. It is known that CYP, drug-metabolizing enzymes such as glutathione S-transferase, N-acetyltransferase 2, and uridine diphosphate glucuronosyl-transferase, drug transporters, and genetic polymorphisms such as human leukocyte antigen are associated with liver injury.[20,21] Typical causative agents include isoniazid, itraconazole, and oral contraceptives.

Chronic DILI

Upon DILI onset, liver damage may persist in 10–20% of cases even after discontinuation of the causative drug; this is considered chronic DILI.[18,21–24] In some cases, autoantibodies, such as antinuclear antibodies, become positive upon DILI onset, making it difficult to distinguish DILI from autoimmune hepatitis (AIH). Drugs that cause AIH-like DILI with positive autoantibodies include minocycline, statins, hydralazine, and nitrofurantoin. Among chronic DILI, persistent DILI is defined by the International Expert Committee in 2011 as "abnormalities in liver markers persisting for more than 3 months in the hepatocellular injury type and more than 6 months in the cholestatic injury type after discontinuation of the causative drug," whereas chronic DILI is defined as "abnormalities in liver markers persisting for more than 12 months regardless of the phenotype of DILI."[24] Chronic DILI may cause drug-induced AIH (DI-AIH), nonalcoholic steatohepatitis-like conditions, vanishing bile duct syndrome, nodular regenerative hyperplasia, peliosis hepatis, and liver cirrhosis (Table 1).[8,22,25] Various drugs may cause fatty liver, the most common of which are tamoxifen, amiodarone, corticosteroids, and tetracycline. Tamoxifen and amiodarone inhibit fatty acid beta-oxidation in hepatocyte mitochondria, resulting in a condition similar to nonalcoholic steatohepatitis. When fatty liver is caused by drugs, the decision to discontinue the drug should be based on the merits of drug continuation and the demerits of liver damage. Weight loss should be promoted through nutritional and exercise therapy, and abstinence from alcohol is recommended.

Cause and epidemiology of DILI

RUCAM is used in all epidemiology reports on DILI internationally. There are no precise data on the incidence of DILI in Japan, but it is thought to be 14–19 persons per 100,000, and approximately 30% of cases are associated with jaundice. In 307 cases (mean age 58 years) of DILI at 27 institutions in Japan from 2010 to 2018, the number of cases caused by antimicrobial agents decreased, whereas that caused by anticancer agents increased. The number of cases caused by health foods is also increasing (Table 2).[26,27] Symptoms include fever in 18%, skin rash in 13%, and eosinophilia in 27% of cases. Regarding pathogenesis, 64% of cases were of the hepatocellular injury type, 15% were of the cholestatic injury type, and 21% were of the mixed type. The duration from initiation of medication to the onset of symptoms was within 7, 30, and 90 days in 19%, 53%, and 79% of cases, respectively, and the drug lymphocyte stimulation test was positive in 36% of cases. In Japan, hepatic failure caused by acetaminophen, which is common in Western countries, is rare. However, the proportion of DILI in patients in a coma and acute liver failure, including late-onset liver failure, has increased: 9.3% in 1998–2003, 14.6% in 2004–2009, and 15.5% in 2010–2015.

Diagnosis of DILI

In the diagnosis of DILI, verification of a causal relationship with the suspected drug is of primary importance. In addition to drugs, folk medicines, health foods, and herbal medicines should also be noted. RUCAM is widely used internationally for the diagnosis of DILI, and has been used in 81,856 cases of drug-induced liver injury reported by mid-2020.[1,28,29] The original version of RUCAM was published in 1993 and has since been revised and an updated RUCAM was proposed in 2016.[30] When using this updated RUCAM, specific operational information should first be noted (Supplementary Table 1). For example, RUCAM affords prospective use, since retrospective scoring is less accurate. Also, RUCAM is only indicated for acute liver injury and not for pre-existing chronic liver disease.

The diagnosis of liver injury is then made when ALT is greater than five times the upper limit of normal or ALP is greater than two times the upper limit of normal. Then, depending on the ratio of ALT to ALP, the liver injury is classified as either acute hepatocellular liver injury, the acute cholestatic or mixed liver injury. Specifically, ALT/ALP≥5 is defined

Table 2. Causative agents of drug-induced liver injury in Japan[26,27]

Agent	1997–2006	2010–2018
Nonsteroidal anti-inflammatory drugs	10%	11%
Antibacterial and antifungal agents	14%	11%
Cancer drugs	3%	10%
Health foods	10%	9%
Gastrointestinal drugs	6%	9%
Psychiatric and neurological drugs	10%	8%
Chinese herbal medicines	7%	6%
Cardiovascular drugs	8%	6%
Hematopoietic and antithrombotic drugs	3%	4%

as hepatocellular injury, ALT≤2 is defined as cholestatic liver injury, and 2< ALT/ALP <5 is defined as mixed liver injury (Supplementary Fig. 1).[30] Each case is diagnosed using the items listed in Supplementary Table 2 for acute hepatocellular liver injury and Supplementary Table 3 for the acute cholestatic and mixed liver injury. For any type of liver injury, seven items are used to score the disease: (1) time to onset from the beginning of the drug/herb, (2) course of ALT (or ALP) after cessation of the drug/herb, (3) risk factors, (4) concomitant drug(s)/herb(s), (5) search for alternative causes, (6) previous hepatotoxicity of the drug/herb, (7) response to unintentional re-exposure. A total score of ≤0 indicates excluded, 1–2 indicates unlikely, 3–5 indicates possible, 6–8 indicates probable, and ≥9 indicates highly probable.[30]

Management of DILI

Common treatment of DILI

When DILI is suspected, the responsible drug should be discontinued. If the patient takes multiple medications, discontinue as many as possible except those essential to treat current diseases. If the patient does not improve after discontinuation of the drug, it is necessary to investigate other causes of liver injury.

Acute liver failure

In Japan, the rate of DILI in patients with acute liver failure is increasing.[31–33] If acute hepatic failure is suspected, as evidenced by jaundice or elevation of prothrombin time, the patient should be admitted to the intensive care unit for close observation. The treatment strategy for acute liver failure due to DILI is similar to that for other causes of acute liver failure: provide support for the failing liver and institute countermeasures against complications. For impaired protein synthesis and coagulation, albumin and fresh frozen plasma should be supplemented; nonabsorbable antimicrobials and synthetic disaccharides should be administered for consciousness disorders. Steroids are empirically used in the treatment of acute liver failure. The steroid dose is generally 0.5–1 mg/kg/day of prednisone or its equivalent. When grade II or higher hepatic encephalopathy develops, artificial liver support should be performed, including plasma exchange and hemodiafiltration. Liver transplantation should be considered if the patient does not respond to medical therapy. For acute liver failure caused by acetaminophen, N-acetylcysteine is effective. The initial dose is 140 mg/kg of N-acetylcysteine, and the maintenance dose is 70 mg/kg every 4 h for 3 days for a total of 18 doses, including the initial dose.

Bile stasis

Ursodeoxycholic acid, which acts as a choleretic, is widely used as a first-line treatment for bile stasis, with few side effects. Taurine can also be used because of its choleretic effect, antioxidant activity, and hepatoprotective. In cases of prolonged bile stasis, supplementation with fat-soluble vitamins, such as vitamin K, is recommended. Phenobarbital is sometimes administered to induce UDP-glucuronosyltransferase expression, which is involved in bilirubin metabolism. Additionally, bile acid sequestrants, such as cholestyramine, treat pruritus caused by hyperbilirubinemia. If treatment is ineffective, steroids may be used, and liver transplantation may be necessary in progressive cases.

DI-AIH

When DI-AIH is suspected based on tests, including autoantibodies and IgG levels, patients with mild hepatic injury can be treated by simply discontinuing the causative drug. If the liver function does not normalize after 3 months, prednisolone may be considered. In patients with moderate or severe liver injury, prednisolone should be administered with discontinuation of the causative drug. In all cases, prednisolone should be discontinued when liver function normalizes. In general, the prognosis of DI-AIH is favorable, and relapse following completion of treatment is rare. However, idiopathic AIH must be considered if relapse occurs after treatment discontinuation.

Difficulties in developing prevention and treatment of DILI

Randomized clinical trials (RCTs) in the prevention and treatment of DILI are difficult to conduct, which limits the development of therapeutic agents. A meta-analysis of 22 RCTs in DILI has revealed the heterogeneity in diagnosis of DILI and research methodology among studies.[34] In addition, it was reported that RUCAM, the internationally most widely used scale for the diagnosis of DILI, was used in only two of eight recent RCTs in DILI.[35] The need for an international research network has been proposed to establish a framework for RCT design and treatment endpoints.

DILI caused by ICIs

Eight ICIs (anti-programmed death-1 [anti-PD-1] antibodies nivolumab, pembrolizumab, and cemiplimab; the anti-programmed death ligand-1 [anti-PD-L1] antibodies avelumab, atezolizumab, and durvalumab; and the anti-CTLA-4 antibody ipilimumab and tremelimumab) targeting three immune checkpoints (PD-1, PD-L1, and CTLA-4) have been approved by the US FDA. In addition, spartalizumab (anti-PD-1

Table 3. Management of immune-related liver injury[48–50]

Grade	Steps
1: ALT or AST>ULN to 3× ULN	Rule out alternate etiologies.
	Monitor liver enzymes every 1–2 weeks.
	Offer supportive care for symptom control.
2: ALT or AST 3–5× ULN	Withhold ICI therapy.
	Check liver function tests, INR, and albumin twice weekly.
	Patients should be advised to stop unnecessary medications and any known hepatotoxic drugs.
	If rising ALT and/or AST when rechecked, start corticosteroids 0.5–1 mg/kg/day.
	Upon improvement, resume ICI therapy after tapering corticosteroids to <10 mg/day.
3: ALT or AST 5–20× ULN	Discontinue ICI therapy.
	Daily liver function tests, INR, and albumin.
	If ALT and/or AST<400 U/L with normal bilirubin, INR, and albumin: corticosteroids 1–2 mg/kg/day.
	If ALT and/or AST>400 U/L or raised bilirubin/INR/low albumin: i.v. methylprednisolone 2 mg/kg.
	If corticosteroid refractory or no improvement after 3 days, may offer mycophenolate mofetil, or azathioprine.
	If no improvement is achieved with corticosteroids or for patients on combination therapy with a novel agent, with standard chemotherapy, or with targeted therapy, refer to a hepatologist for further pathologic evaluation of hepatitis.
	Corticosteroid taper should be attempted over a period of 4–6 weeks; re-escalate if needed.
4: ALT or ALT>20× ULN	Discontinue ICI therapy.
	Daily liver function tests, INR, and albumin.
	i.v. methylprednisolone 2 mg/kg.
	If corticosteroid refractory or no improvement after 3 days, may offer mycophenolate mofetil.
	Should refer to hepatology if no improvement is achieved with corticosteroid.
	Corticosteroid taper should be attempted over a period of 4–6 weeks when symptoms improve to grade ≤1, re-escalate if needed.
	Consider transfer to tertiary care facility if necessary.

ICI, immune checkpoint inhibitor; ULN, upper limit of normal.

antibody) is currently in development. ICIs have been used to treat several cancers in recent years; however, hepatotoxicity is one of its most frequent immune-related adverse events (irAEs). The mechanism of hepatotoxicity as an irAE is different from that of DILI and is thought to be related to excessive autoimmunity caused by ICI. In most cases of ICI-induced liver injury, infiltration of CD8-positive T cells is observed, and these lymphocytes activated by ICI are thought to be the primary cause of liver injury (Supplementary Fig. 2).[36] The incidence of DILI due to ICI was reported to be 0.8–14.6% for the CTLA-4 inhibitor ipilimumab and 2.7–16% for PD-1/PD-L1 inhibitors such as nivolumab.[37–43] Swenson *et al*.[44] reported that in a retrospective analysis of 112 patients treated with durvalumab, an anti-PD-L1 antibody, 19% were diagnosed with DILI by RUCAM. The risk of DILI is higher when ICIs are concomitantly used with other ICI or chemotherapeutic agents. In DILI due to ICI, hepatocellular injury is the most common type, but cholestatic and mixed types have also been reported.[45] Although the onset of DILI due to ICI usually ranges from 1 to 3 months after initiation of treatment, it may also develop after a prolonged period or following ICI discontinuation. Additionally, sclerosing cholangitis caused by ICI was reported as a unique type of liver injury.[46] This type is characterized by elevated biliary enzymes, focal bile duct dilatation without obstructing extrahepatic bile ducts, and diffuse thickening of the bile duct wall. According to a meta-analysis of 122 trials, the number of deaths due to hepatitis as an irAE was 5/5,368 (0.09%) with an anti-CTLA-4 antibody, 0/9,136 (0%) with an anti-PD-1 antibody, 1/3,164 (0.03%) with an anti-PD-L1 antibody, and 2/1,549 (0.13%) with the combination of an anti-PD-1 antibody/anti-PD-L1 antibody and an anti-CTLA-4 antibody. These results suggest that liver damage as an irAE is often nonfatal.[47] It should be noted in this section that there is not a large enough data set on this topic and some studies have been included that do not describe the use of RUCAM in assessing immunotherapy-induced hepatotoxicity.

The severity of the hepatic injury is determined using the Common Terminology Criteria for Adverse Events defined by the National Cancer Institute. Table 3 summarizes the responses to immune-related liver injury recommended in the guidelines of the European Society of Oncology, the

European Society of Hepatology, and the American Society of Clinical Oncology.[48–50] In Grade 2 hepatotoxicity, the responsible drug should be temporarily discontinued. Liver function tests, INR, and albumin are checked twice weekly. If ALT and/or AST are elevated on reassessment, corticosteroids 0.5–1 mg/kg/day should be started. In patients with Grade 3 or higher hepatotoxicity, discontinuation of the drug is recommended. If ALT and/or AST are less than 400 U/L and bilirubin, INR, and albumin are normal: corticosteroids 1–2 mg/kg/day should be administered. Also, if either ALT or AST is greater than 400 U/L, bilirubin or INR is elevated, and albumin is decreased, methylprednisolone 2 mg/kg/day should be administered intravenously. In patients with Grade 4, discontinuation of the drug and intravenous administration of methylprednisolone 2 mg/kg is recommended. Furthermore, if steroids are ineffective or there is no improvement after 3 days, mofetil mycophenolate may be administered. Mycophenolate mofetil is commonly used to prevent graft rejection in organ transplantation and may be administered in various irAEs. Tocilizumab, tacrolimus, azathioprine, cyclosporine, and antithymocyte globulin are also options.[48–50] Thus, most guidelines recommend permanent discontinuation of ICI in high-grade immune-related liver injury. However, recent reports indicate that rechallenge is possible after recovery from liver injury.[51] For patients who have no other treatment options, this may allow them to continue treatment, Further reports into this topic are expected.

Conclusions

To diagnose DILI, it is important to obtain a detailed history of drug intake, including health foods, and determine the disease type. The updated RUCAM is widely used in the diagnosis of DILI, and there are numerous reports that demonstrate its usefulness. In addition, conducting appropriate monitoring, such as periodic liver tests, when administering new, long-term, or high-risk drugs should be performed and updated on information regarding a drug's side effects.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Conception and design (TK, MY), administrative support (TK, MY), provision of study materials or patients (TK, MY), collection and assembly of data (all authors), data analysis and interpretation (TK), and manuscript writing (all authors). All authors have made a significant contribution to this study and have approved the final manuscript.

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