Idiosyncratic DILI: Immunology in Cases with Evidence Based on RUCAM

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Abstract: Idiosyncratic drug induced liver injury (iDILI) is a multifaceted and fairly well described liver disease, but there is yet some uncertainty on the role of immune systems triggering the liver injury and speculation on the cascade of immune events. Many conclusions were so far based on narratives or cases of iDILI, which did not receive the benefit of a robust causality assessment like by the Roussel Uclaf Causality Assessment Method (RUCAM). This analysis aims to clarify the cascade of immune events that lead to the liver injury by conventional drugs. For this approach, the search focused on iDILI cases with verified diagnosis by RUCAM. Most promising were parameters obtained from the blood as mirror of what happened in the liver during the injurious processes.The focus of this present analysis is on patients with RUCAM based iDILI and concomitant immune-related parameters in the blood. As an example, compelling evidence for a role of immune systems in iDILI was found for circulating mediators in the blood secreted by liver immune cells in patients under a therapy for tuberculosis, detected were also serum anti-cytochrome P450 (CYP) antibodies in patients after anesthesia with sevoflurane or desflurane and thereby reflecting their metabolism by the CYP 2E1 isoform, the occurrence of serum of autoantibodies in patients with drug induced autoimmune hepatitis (DIAIH) due to many drugs, and the role of blood and liver monocytes, which provide direct evidence for the activation of the hepatic innate immune system to the adapted immune system. In essence, patients with RUCAM based iDILI show various immunology features in the blood compatible with the role of the hepatic immune systems in patients with suspected iDILI caused by some but not all drugs.

Keywords: Immunity, Autoimmunity, Hepatic immune cells, Idiosyncratic drug induced liver injury, RUCAM, Cytochrome P450, HLA B*57:01, Immune-mediated hypothesis.

1. INTRODUCTION

Idiosyncratic drug induced liver injury (iDILI) by multiple drugs and drug classes is a complex disease [1-4], carefully discussed under the aspects of causality assessment using the Roussel Uclaf Causality Assessment Method (RUCAM) as its original of1993 [5,6] or its updated version of 2016 [7]. Similarly, the updated RUCAM was applied in iDILI cases due to rosuvastatin [8], tyrosine- kinase inhibitors [9], teriflunomide [10], tigecycline [11], potassium para aminobenzoate [12], androgenic anabolic steroids [13], atezolizumab [14], durvalumab [15], memantine [16], with several drugs in the elderly [17], in newborns and children [18], and in a Brazil hospital pharmacy setting [19].

RUCAM was published as a novel method to assess causality in iDILI, based on the conclusions of international consensus meetings with attending DILI experts from Denmark, France, Germany, Italy, UK, and the USA [5,6]. Using iDILI cases with positive reexposure tests serving as a gold standard, RUCAM was well validated [6] and is a means of assigning points for clinical, biochemical, reexposure, and serologic features as well as search for non-drug causes [5-7].Summing up the individual scores derived from each key element provides final causality gradings: score ≤0, excluded causality; 1–2, unlikely; 3–5, possible; 6–8, probable; and ≥9, highly probable, which reflects the likelihood that the hepatic injury is due to a specific medication [5,7]. As a result, RUCAM represents a diagnostic algorithm for objective, standardized, and quantitative causality assessment. It is applied throughout the world and highly appreciated, being user friendly, cost effective with results available in time and without need of expert rounds that commonly provide subjective and arbitrary opinions.

In some of the RUCAM related reports [1-4,8-19], the issue of specific human leucocyte antigens (HLA) allele variability was mentioned, which are under discussion being involved as genetic factors in causing the liver injury. In addition, immune mechanisms may play a role in iDILI, but proposals were mainly based on narratives rather than on iDILI cases with established causality assessment like RUCAM [5-7], which helps find and exclude alternative commonly found among published cohorts of patients with iDILI [7]. If not detected in time, alternative causes confound the

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diagnosis of suspected iDILI, classifying the cases erroneously as unrelated to drugs.

The aim of this report is to clarify the cascade of immune events that leads to the liver injury. For this approach, the search focused on iDILI cases with verified diagnosis by RUCAM. Most promising were parameters obtained from the blood as mirror of what happened in the liver during the injurious immune processes.

2. SEARCH TERMS AND STRATEGY

The literature search strategy involved the PubMed database and Google Science, using the following terms:idiosyncratic drug induced liver injury; RUCAM; Roussel Uclaf Causality Assessment Method; immunology: immune cells, antibodies; and combinations thereof. The first 20 publications derived from each term group were checked for their suitability to be included in this review article and provided the primary base for further analysis. The search was finalized on 25 August 2023. Publications were complemented from the large private archives of the author. Limited to publications in English language, there were no other restrictions regarding year of publication or study design.

3. BASICS OF HEPATIC IMMUNOLOGY HOMEOSTASIS

The liver has critical metabolic and clearance functions, taking up nutrients and pathogens from the blood [20]and is the largest solid human organ with immune properties [21], helping reduce liver injury elicited by-bacteria, viruses, toxins, drugs, and antigens entering the body via inhalation, through the skin, or most importantly via the intestinal tract. Immune reactions in the liver commonly protect the human body from health hazards, but occasionally they provoke severe diseases [22,23] or are targets for therapy [24]. The liver can take up immune cells from the blood or produce them itself [22]. As a result, it harbors many immune cells with various qualities through mediators, which they secrete and allow for crosstalk with other cells in the liver. Hepatic immune cells can be classified as following:(1) Kupffer cells (KCs) secreting proinflammatory cytokines like the interleukins (ILs) IL-1, IL-6, and Tumor necrosis factor (TNF-α) as well as chemokines such as MKIP-1α and RANTES [22,26]; (2) monocytes (MCs) providing TNF-α, the interleukins IL-1β, IL-6, and IL-8, the chemokines CCL1, CCL2, CCL3, and CCL5, as well as growth factors such as granulocyte colony-stimulating factor (GCSF) and macrophage colony-stimulating factor(MCSF)[27];(3) hepatic stellate cells (HSCs)producing cytokines and growth factors capable of stimulating various hepatic cell types including TGFα, TGFβ, epidermal growth factor (EGF), hepatocyte growth factor (HGF), platelet-derived growth factor (PDGF), stem cell factor, acidic and basic fibroblast growth factor (FGF), macrophage colony-stimulating factor, and platelet activating factor [28,29];(4) hepatic dendritic cells (HDCs)generating proinflammatory cytokines like IL-2, IL-6, IL-12,TNF-α, and INF-γ[30,31];(5) hepatic B cells (BCs)releasing the proinflammatory cytokines interferon (INF)-γ and TNF-α [32];(6) hepatic T cells (TCs) secreting TNF-α, TGF-β, IL-10, and IFN-γ [33,34]; and (7) liver sinusoidal endothelial cells (LSECs) releasing chemokines and cytokines including IFN-γ[35,36].

4. HEPATIC IMMUNOLOGY IN RUCAM BASED IDILI

4.1. Mandatory use of RUCAM to Assess Causality and to Exclude Alternative Causes

Abundant immune cells with their secreted mediators presumably trigger various liver diseases of different etiologies [22-36]but a firm diagnosis thereof must be ascertained. This also applies to DILI, which is confrontedby multiple alternative causes that potentially confound the diagnosis of DILIin a normal clinical and ambulatory setting [7], a phenomenon known among DILI experts since1990 reports [37,38]. Inaddition,due to lacking a robust and accepted causality assessment, inaccurate DILI diagnoses were also uncovered among suspected DILI cases of the problematic LiverTox database [39-41]. Compiled in two analytical reports on published DILI cases, which were assessed for causality using RUCAM in virtually all cases, there were incomplete data sets and various alternative causes as confounders, putting the initial diagnosis of suspected idiosyncratic DILI in question due to missed diagnoses (Table **1**) [37,38].

The role of RUCAM in search for alternative causes of suspected iDILI published worldwide (Table **1**) [37] was underscored in the recent Taiwan report, based on an excellent analytical approach [38]. In this cohort, only iDILI cases were considered with an at least probable RUCAM causality grading, also excludingcases of HILI and poor-quality data DILI cases with incomplete clinical reports (Table **1**). Alternative causes were found worldwide in

Table 1: Alternative Causes found among Suspected Idiosyncratic DILI Cohorts

Specified alternative causes [37]	Frequency (%)
Biliary diseases	11.89
Autoimmune hepatitis	10.67
Hepatitis B or C	8.54
Tumor	7.93
Ischemic hepatitis	7.32
Systemic sepsis	6.10
Hepatitis E	5.79
Liver injury by other comedication	5.79
Virus Hepatitis	5.49
Past liver transplantation	5.18
Alcoholic liver disease	4.88
Fatty liver	2.44
Non-alcoholic steatohepatitis	2.44
Hepatitis C	1.83
Cardiac hepatopathy	1.52
Thyroid hepatopathy	1.22
Primary sclerosing cholangitis	0.92
Primary biliary cholangitis	0.92
Gilbert syndrome	0.92
CMV Hepatitis	0.61
EBV Hepatitis	0,61
Hemochromatosis	0.61
Wilson disease	0.61
Paracetamol overdose	0.61
Postictal state	9.61
Osseous disease	0.61
Lymphoma	0.61
Preexisting liver cirrhosis	0.61
Hepatitis B	0.31
Benign recurrent intrahepatic cholestasis	0.31
Rhabdomyolysis	0.31
Polymyositis	0.31
Chlamydial infection	0.31
HIV infection	0.31
Total	100%
Specified alternative causes [38]	**Frequency (%)**
Co-medicated herbs causing HILI	37.19
Intrinsic DILI by acetaminophen	23.12
Incomplete clinical or laboratory data	21.61
Systemic diseases causing abnormal LTs	7.04
HBV carrier without other serology data	6.03
Acute hepatitis with positive IgM AB	5.03
Total	100%

Data were compiled from previous analytical reports of iDILI cases, virtually all of them were assessed for causality by RUCAM [37,38]. Abbreviations: AB, antibodies; CMV, Cytomegalovirus; DILI, drug induced liver injury; EBV, Epstein-Barr virus; HBV, Hepatitis B virus; LTs, liver tests; RUCAM, Roussel Uclaf Causality Assessment Method.

4556/13,336 cases of suspected iDILI (34.2%) with values of up to 50%[37], while in the Taiwan study there were 199/1213 alternative causes plus non-assessable cases described in suspected iDILI (16.4%) [38]. As a result, 1014 eligible cases of iDILI were recorded [38], which can easily be added to the 81,856 iDILI cases, published worldwide from1993 until mid-2020 and all assessed for causality by RUCAM [42].

4.2. Search for Immunity Characteristics in RUCAM Based Cases of Idili

4.2.1. General Aspects

Studying the role of immunology in iDILI requires cases of iDILI with a robust diagnosis verified by an accepted causality assessment method such as RUCAM [5-7]. Of interest for analysis were iDILI patients with circulatory immune mediators secreted by hepatic immune cells found in the blood, cases with serum antibodies against hepatic microsomal cytochrome P450 (CYP), blood autoantibodies resulting from metabolic interactions of drugs with hepatocytes and non-parenchymal cells of the liver including hepatic immune cells,cases of iDILI associated with clinical signs of extrahepatic immunology like the skin, and therapy modalities with corticosteroidsfor the immune-triggered liver injury.

4.2.2. Common Circulatory Immune Mediators

Using commercially available kits, circulatory mediators like the cytokines IL-22, IL-22 binding protein (IL-22BP), IL-6, IL-10, IL-12p70, IL-17A, IL-23, IP-10, or chemokines like CD206 and sCD163 were quantified in the plasma of patients with the diagnosis of DILI caused by anti-tuberculosis drugs and verified by prospective use of the updated RUCAM that provided high causality gradings [43]. These data provide direct and compelling evidence of an immune role in triggering iDILI by these anti-tuberculosis drugs, but similar results in patients with iDILI by other drugs are currently not found in the literature.

4.2.3. Serum Antibodies against Hepatic Microsomal CYP Isoforms

Additional strong evidence for the involvement of the immune system in the development of iDILI was provided byantibodies against CYP isoformsfound in the serum of patients with RUCAM based iDILI due to a limited number of drugs: sevoflurane and deflurane (Table **2**) [44-46].

With iDILI diagnosis verified by RUCAM, sevoflurane and deflurane (Table **2**) are among the 58.3% of drugs, implicated in triggering iDILIand metabolized by CYP isoforms, whereas the remaining drugs undergo metabolism through other pathways [47]. Fascinating is the clinical observation that the use of drugs, which are substrates and metabolized by CYP isoforms, leads to the generation of antibodies against cytochrome P450 (CYP), found in the serum of patients with iDILI (Table **2**). This is an excellent biological example how information of hepatic immune processes connected with iDILI is released in the blood, ready to be analyzed for further mechanistic steps related to immunology issues of the liver injury [45-48]. In more detail, serum anti-CYP 2E1 antibodies were found after use of the volatile anesthetic sevofluranein four patients with iDILI and verified diagnosis by using RUCAM, which led to RUCAM based causality gradings of highly probable in all cases [45]. These results were confirmed by following data

Table 2: Serum anti-CYP 2E1 antibodies in patients with RUCAM-based iDILI following use of volatile anesthetics

Immune parameter	Details of RUCAM-based iDILI cases	Drug	First author
Serum anti-CYP 2E1	Patients with iDILI by the volatile anesthetic sevoflurane showed positive serum titers of anti-CYP 2E1 in cases with highly probable causalities and well-described clinical features including fever, flu-like symptoms, jaundice, vomiting, right upper quadrant abdominal pain, reduced appetite, rash, and myalgias after the second anesthesias. Liver histology showed centrilobular necrosis with hemorrhage as well as rosetting of liver cells.	Sevoflurane	Nicoll, 2012 [45]
Serumanti-CYP 2E1	Detailed clinical description of RUCAM-based iDILI case caused by a combination of volatile anesthetics. Special care was taken considering alternative causes such as hypotension and DILI by antibiotics or paracetamol.	Sevoflurane + desflurane	Bishop, 2019 [46]
Serum anti-TFA	Most exciting, in some patients with RUCAM-based iDILI, trifluoroacetyl (TFA) halide as toxic intermediates were detected, arising from drug metabolism via CYP 2E1 and providing the potential of protein adduct formation and free radical generation, conditions resulting in detectable anti-TFA antibodies.	Sevoflurane + desflurane	Nicoll, 2012 45] Bishop, 2019 [46]

This table is derived from a previous open access article [44]. Abbreviations: CYP, Cytochrome P450; DILI, drug-induced liver injury; RUCAM, Roussel Uclaf Causality Assessment Method; TFA, Trifluoroacetyl.

obtained for sevoflurane and desflurane, another modern volatile anesthetic, whereby sevoflurane was used mostly alone and rarely combined with desflurane [46]. Five patients with iDILI reached a RUCAM score of ≥6, and serum anti-CYP 2E1 antibodies were found in three patients with RUCAM scores of 12, 7, and 6, whereas in two patients with RUCAM scores of 12 and 7, anti-CYP 2E1 antibodies were not detected in the serum [44-46].As a result, only part of the RUCAM based iDILI cases were associated with these antibodies, while additional analysis revealed that anti-CYP 2E1 antibodies were detected unexpectedly in patients, who were exposed to the anesthetics but did not fulfill the RUCAM criteria of iDILI, thereby not providing a homogenous antibody picture [44,46]. Besides, the data of this analysis are highly appreciated as of robust quality andsince the evaluating group published an excellent external interrater performance for their use of RUCAM [46] confirming previous reports on external interrater qualification in favor of RUCAM [49,50] and on internal interrater performance [6].

For reasons of completeness, other drugs are to be mentioned, because they function as known substrates of hepatic microsomal CYP isoforms, are metabolized by CYPs, and can trigger suspected iDILI, but none of these iDILI cases received the benefit of causality assessment by RUCAM [44], a major flaw in face of many alternative causes not related to drug treatment (Table **1**) [37,38]. Among the drugs under critical discussion are halothane (causing serum anti-CYP 2E1 antibodies) [51-57], isoflurane (anti-CYP 2E1) [57], isoniazid (anti-CYP 2C9) [48], dihydralazine (anti-CYP 1A2), tienilic acid (anti-CYP 2C9), and antiepileptics (anti-CYP 3A) [51].

The association of serum anti-CYP isoforms with iDILI by sevoflurane and desflurane suggests an immunological involvement in this process but not necessarily a causal immune relationship between CYP and the liver injury [44]. In fact, liver injury by drugs such as sevoflurane and desflurane is also associated with the formation of trifluoroacetyl (TFA) halide as toxic intermediates [45,46] that form protein adducts and may generate free radicals, known as reactive oxygen species (ROS) [45, 57-59]. This is accompanied by anti-TFA antibodies detected in the serum of some but not all patients with liver injury by volatile anesthetics [57,58]. Serum anti-CYP antibodies in connection with iDILI were reported only for a few CYP dependent drugs, leaving aside many of the drugs metabolized by CYPs that do not generate these antibodies for unknown reasons. The lack of antibody data can be real, alternatively, no comprehensive analytical approaches were done. To solve this issue, future studies should focus on detection of serum anti-CYP antibodies, considering specifically drugs metabolized by CYPs and causing iDILI with valid diagnosis ascertained by using the updated RUCAM and high RUCAM based causality gradings of probable or highly probable.

4.2.4. Serum Autoantibodies

Anti-nuclear antibodies (ANA), anti-smooth muscle antibodies (ASMA), and rarely other autoantibodies that might be detected in the serum of patients treated with conventional drugs, who experienced liver injury addressed for causality using RUCAM [60,61]. For instance, among a cohort of 139 RUCAM based iDILI patients, serum ANA results were positive in 95 patients (68.3%) and negative in 44 patients (32.7%), but data remain open for discussion since cases with a possible causality grading were included, herbal and dietary supplements were among the DILI patients, and the original RUCAM was used lacking exclusion of HEV rather than the updated RUCAM [60]. In 71% of these cases ANA and/or SMA titers were positive. In the other earlier RUCAM based study, similar data were reported in addition to normal values of immunoglobulins IgA, IgG, and IgM [61]. These two RUCAM based studies on serum ANA and SMA suggest immunology reactions in the liver of some but not all patients with iDILI.

4.2.5. Blood and Liver Monocytes

Monocytes helped provide direct evidence for a role of the innate and adaptive immune system in iDILI with RUCAM based verification of the diagnosis. In general, the initiation of an immune response in iDILI presumably requires the activation of antigen presenting cells (APCs) by molecules such as danger-associated molecular pattern molecules (DAMPs) [62]. Direct evidence for the involvement of the innate immune system in the iDILI was convincingly shown with causative drugs such as diclofenac, indomethacin, levofloxacin, and phencoumon by studies of monocyte-derived hepatocyte-like cells in iDILI cases assessed by the updated RUCAM [63]. These results support the assumption that monocytes are part of the innate immune system [62,64-66]. Going back to the origin, hepatic monocytes are commonly derived from bone marrow progenitors, released into the blood before they enter the liver, where they differentiate into liver resident macrophages such as KCs and infiltrating

monocyte-derived macrophages (MoMF), allowing for crosstalk with hepatic monocytes within the liver and intensive exchange of inflammatory mediators [66].

4.2.6. Drug Induced Autoimmune Hepatitis

Direct evidence for the involvement of the hepatic immune system in iDILI wasalso provided in one of its subgroup by studies on cases of drug induced autoimmune hepatitis (DIAIH), all assessed for causality using RUCAM to establish the diagnosis of autoimmune DILI syn DIAIH, caused by several drugs as examples [67]: antimicrobials [68,69], atorvastatin [67], augmentin [68], ceftriaxone [68], diclofenac [70], direct oral anticoagulants [71], hydralazine [70], infliximab [72,73], isoniazid [70], ketoprofen [68], minocycline [70], methyldopa [70], nimesulide [68], nitrofurantoin [70,72,74,75], non-steroidal anti-inflammatory drugs [68,71,74,76], sorafenib [67], and statins [69,71,75]. The studies discussed above provided a clear differentiation of DIAIH from the classical genuine AIH by using scores of the simplified AIH scale for assessing the AIH [77] and applying the scores of RUCAM [5,7] for evaluating DIAIH [67]. Similar proposals were made for cases in pediatrics [78], enforcing now the use of the updated RUCAM for suspected DIAIH [7]. Apart from triggering DIAIH, some of these drugs may also cause common DILI without signs of autoimmunity, as noted by one study [72] and confirming previous statements [62].

4.2.7. Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

The Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) caused by a small group of drugs in a few patients with RUCAM based iDILI provided direct evidence for an involvement of the immune system in the liver injury DILI [79,80]. Causality of idiosyncratic DILI was evaluated by RUCAM and of SJS/TEN using the Algorithm for Drug Causality for Epidermal Necrolysis, which was highly probable or probable in all cases [79]. SJS/TEN are mediated by TCs, whereby drugs may initiate immunological responses via a hapten/ pro-hapten process with covalent binding of small-molecule drugs to proteins [80]. Serum granulysin could play a role as diagnostic biomarker and initiator of the disease, in association with various cytokines and chemokines with special reference to IL-15 [80,81].

4.2.8. HLA Association with iDILI

Genetic human leucocyte antigen (HLA) alleles are associated with RUCAM based iDILI by drugs like amoxicillin-clavulanate [82-85], carbamazepine [82], dapsone [85], enalapril [86], erythromycin [86], fenofibrate [86], flucloxacillin [82,87-89], flupirtine [90], infliximab [91], isoxazolyl penicillins [82], methimazole [92], methyldopa [86], minocycline [93], nitrofurantoin [94], sertaline [86], terbinafine [86], ticlopidine [86], and trimethoprim-sulfamethoxazole [95]. Despite this overt association, a firm causal relationship between HLA alleles and immunity of iDILI has not yet clearly been established and await further studies. In addition, drugs like atorvastatin and other statins, azathioprine and other thiopurines, ciprofloxacin and other fluoroquinolones, diclofenac, fasiglifam (TAK-875), interferon beta, isoniazid, and nimesulide implicated in iDILI lack any HLA association [96,97].

4.2.9. Immune Association as Evidenced Bymodulation by Glucocorticoids

In support of the immune involvement, DIAIH responds well to the immune modulatory action of glucocorticoid treatment without relapse after treatment cessation, whereas relapse in genuine AIH is common and characteristic for this disease [67,71]. Notably, glucocorticoids are only partially effective in treating unselected idiosyncratic DILI caused by various drugs as a whole DILI cohort, suggesting that not all DILI cases are triggered by immune mechanisms [48] in line with previous proposals [64 89]. Direct evidence for an involvement of the immune system in idiosyncratic DILI was also provided by its rare association with the immune-triggered Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) caused by a small group of drugs [79]. Causality of idiosyncratic DILI was evaluated by RUCAM and of SJS/TEN using the Algorithm for Drug Causality for Epidermal Necrolysis, which was highly probable or probable in all cases.

5. CONCLUSIONS

The analysis of published data of immune features derived from RUCAM based cases of iDILI show immune characteristics at various levels that allow for a tentative view of mechanistic steps leading to the liver injury: (1) drugs enter the hepatocytes and most of them bind to the smooth endoplasmic reticulum, which corresponds to the microsomal fraction of biochemists, where the drug may be metabolizes to reactive intermediates. These metabolites and/or the parent drug trigger a covalent binding with structural membrane proteins, a process that leads to the generation of hapten-protein configuration. Evidence for this initial mechanistic step is provided by positive

serum anti-CYP antibodies of patients with RUCAM based iDILI; (2) drugs that are not substrates of CYP may be metabolized by other systems involving enzymes like flavoproteins; (3) hapten-proteins may stimulate immune cells in the liver, which secrete cytokines and chemokines, able to crosstalk with each other and the liver immune cells as evidence based on detectable circulating mediators in the blood in patients with iDILI assessed by RUCAM; (4) Blood monocytes will invade the injured liver, shown by clinical studies on patients with RUCAM based iDILI; (5) detection of autoantibodies in the serum of patients with RUCAM based iDILI provides further evidence for a role of the hepatic immune systems, which needs transformation from the innate immune system into the adaptive immune system; (6) HLA alleles involved in immune processes of iDILI are found for some implicated drugs, not found for a small group of drugs, and not assessed for a large group of drug; (7) the association of RUCAM based iDILI with the immune Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) and the observed immune mediators in the serum provides clear evidence of the immune involvement in the development of iDILI; (8) efficacy of corticosteroid treatment in some patients with RUCAM based iDILI suggests that immune mechanisms were involved in these cases; and finally, (9) it is evident that for many drugs implicated in causing iDILI immunology features were not search for, and in some patients with RUCAM based iDILI, no immunology parameters were found, leading to the conclusion that non-immune mechanisms may also play a role among the iDILI cohort, substantiating lack of homogeneity regarding immuneaspects in the liver injury.

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CONFLICT OF INTERESTS

The author states that he has no conflict of interests with regard to this article.

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