Editorial

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Drug induced liver injury and its relationship to autoimmune hepatitis

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Drug-induced liver injury (DILI) is a leading cause of acute liver failure [1] and is of major importance to the pharmaceutical industry, as it is the most frequent reason for withdrawal of substances from the market. More than 1000 different drugs and herbal remedies have been described to cause DILI. Some drugs cause a dose-dependent toxicity which can be anticipated – a well known example is acetaminophen. The vast majority of DILI cases cannot be foreseen and are, therefore, termed idiosyncratic. Oxidative stress, reactive metabolites, mitochondrial toxicity, modulation of drug metabolizing transporters, induction of apoptosis or necrosis, as well as immunoallergic reactions to protein adducts may all be involved in DILI, but for most of the drugs the specific mechanisms contributing to DILI are unknown [2]. A classification of hepatocellular, mixed or cholestatic liver injury is used in the clinic to describe damage and severity of liver injury but its value in predicting the outcome of DILI is unclear. DILI can range from asymptomatic elevation of liver enzymes to fulminant hepatic failure [1]. Its over-all mortality depends on the drug used, the timely detection of DILI including the appropriate action taken, as well as individual cofactors and comorbidities such as the presence of diabetes mellitus [3]. Mortality rates of approximately 10% [1] have been reported but may be highly overestimated since most mild drug reactions will not be registered. In most patients, DILI leads to a complete recovery. However, up to 1% of all patients with DILI may develop liver cirrhosis subsequently [4].

DILI is a rare event with an estimated incidence of 1 per 10,000 to 1 per 100,000 treated patients [5]. Some risk factors have been identified: the daily amount of the drug causing the reaction (intake of >50 mg daily increases risk), a predominantly hepatic metabolism of the drug (>50%) [6], and mitochondrial dysfunction that may be the underlying cause of the increased risk of DILI in diabetes patients [7]. Genetic polymorphisms within genes relevant to drug metabolism [8] are being identified and may be used to stratify the risk of DILI to certain drugs in the future.

A question relevant to daily clinical practice is, if re-exposure to the same or to other drugs may cause a second DILI episode. Re-exposure to the same drug generally should be avoided due to the considerable mortality rate reported after re-exposure to drugs such as halothane (up to 50% due to a combination of mitochondrial and immune-mediated injury) [9]. Nonetheless, for drugs that are urgently needed in case of life threatening disease, such as in tuberculosis, careful re-exposure can be undertaken after the resolution of the first DILI episode with acceptable risk [10]. The risk of re-exposure to a different drug that may belong to the same class of drugs or be completely unrelated is not well studied. To this end, the study presented by Lucena *et al.* in this issue adds valuable and reassuring information [11]. In this study, the Spanish DILI registry of patients with probable or highly probable idiosyncratic DILI was searched for patients who suffered from a second DILI episode. Only a small number of patients (9 patients, 1.21%) from the cohort of patients with prior DILI developed a second episode of liver injury and none of the patients' required liver transplantation or had a fatal outcome. Of particular interest, the majority of patients (8 out of 9) experiencing a second DILI episode had a similar (hepatocellular) damage pattern. The drugs responsible for the second DILI episode were structurally related to the drug of the first DILI episode in 4 out of 9 cases and, in 2 cases, the target of the drug was the same. This may point toward an immune-mediated drug injury directed against similar protein adducts forming haptens. Indeed, 4 out of the 9 patients (44%) were diagnosed with so called "autoimmune (AIH) DILI" since these patients fulfilled the criteria for probable or definite AIH, according to the revised and simplified score of the international autoimmune hepatitis study group [12,13]. This number was considerably higher than in patients with a first DILI episode, where only 12/733 (1.6%) patients were diagnosed with "AIH DILI" [11], suggesting that immune-mediated reactions become the main mechanisms leading to DILI after re-exposure to different drugs.

There is no consensus on the nomenclature of immune-mediated DILI and we will propose some definitions and respective diagnoses at the end of this article. Until then, the diagnoses given in the publications cited will be used.

In clinical practice, the differentiation between immune-mediated DILI and AIH may be challenging. There are no pathognomonic features of AIH and the diagnosis is made according to a clinical, biochemical, serological, and histological pattern which has to be confirmed by the response to immunosuppressive treatment [14]. This difficulty in differentiating between AIH and drug

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Table 1
DILI and AIH: suggested diagnoses and clinical characteristics.

	Characteristics
AIH with DILI	Patients with known AIH; probably chance association; often advanced fibrosis on histology
Drug-induced AIH	Patients with unrecognized AIH or predisposition to AIH, in whom AIH is unmasked or induced by DILI; good response to steroids; relapse after withdrawal of immunosuppression with the need for continued immunosuppressive treatment; chance association of drug intake in a patient with first presentation of AIH cannot be ruled out
Immune-mediated DILI	Clinical, biochemical, and histological signs similar to AIH; eosinophilia and rash may be present; usually no advanced fibrosis; good response to steroids; remission is maintained after successful withdrawal of steroids

induced immune-mediated liver injury has been recently highlighted by the study of Björnsson *et al.* [15] demonstrating that in a large cohort of AIH patients, 9.2% suffered from "drug induced AIH". There was no difference in histology or serological findings and treatment response was similar between AIH cases and "drug induced AIH". However, there were no relapses in "drug induced AIH" in those patients in whom immunosuppression was discontinued. This stands in contrast to the high relapse rate after withdrawal of immunosuppression in AIH (65% in this study), which in most cases remains a chronic disease [14]. Of note, it has recently become clear that histological centrilobular necrosis can be seen both in DILI as well as in acute AIH [15]. Likewise, auto-antibodies typically seen in AIH are sometimes present in acute liver injury of varying causes and should, therefore, be interpreted with caution [16].

In the following, we would like to address various combinations of DILI and AIH and to suggest appropriate diagnoses (Table 1). There are several possible connections between DILI and AIH.

The first is that a patient with known AIH experiences DILI. Whether this occurs more frequently than in other patients is unknown. Liver histology will often reveal advanced fibrosis in these patients, which should be termed "AIH with DILI".

The second is that a patient has low grade AIH that has not been diagnosed before or even just the predisposition to AIH that is unmasked by DILI. The release of hepatic antigens and consecutive presentation of these autoantigens by immune cells may lead to a continued – autoagressive – immune reaction in genetically susceptible individuals. In a long term follow-up study of 685 patients with DILI and jaundice, from Sweden, 23 patients had been hospitalized for liver disease and 5 of these were diagnosed with AIH after a mean of 5.8 years [4]. These mechanisms may also be true for drugs interfering with cytokines such as anti-TNFα [17] or β-Interferon [18]. In screening case reports and case series, many of these patients developed "true" AIH with a permanent need for immunosuppression. Therefore, these patients suffer from "drug-induced AIH". However, a chance association of drug intake in a patient with previously unknown AIH cannot be ruled out in these patients and in some, the symptoms of AIH may even be the reason for taking the drug.

Thirdly, there are a number of drugs that are well known to cause immune-mediated DILI. These are patients with hepatocellular or mixed type of damage that do not improve after cessation of the causative drug and frequently, but not always, present with fever, eosinophilia, lymphadenopathy, and rash. These patients may be indistinguishable from AIH by their clinical, laboratory, and histological presentation and by their good response to immunosuppressive treatment. In our experience, prominent eosinophilic infiltrates may sometimes point toward DILI in these cases. Among the drugs causing immune-mediated DILI are antimicrobials such as nitrofurantoine and minocycline [15]. In these patients, the early initiation of high dose steroid treatment may be life saving. Of particular importance, unlike in true AIH, most of these patients do not need permanent immunosuppression as they usually have sustained remission without relapse after the initial treatment [15]. In line with this hypothesis, HLA-associations have been identified for several antimicrobials causing immune-mediated DILI, such as flucloxacillin and amoxicillin/clavulanate [19], which are unrelated to the HLA haplotypes associated with AIH. Since these cases do not develop AIH with a relapsing remitting course, we would suggest to call these "immune-mediated DILI", and not to use the term autoimmune.

So what do we learn for patient care? A second DILI involving a different drug is a rare event but if it happens, immune-mediated DILI is common. Differentiating immune-mediated DILI from AIH is difficult as the presentation may be the same. Liver histology should be performed and eosinophilia may point toward DILI, whereas centrilobular necrosis cannot be used to differentiate the two. Prompt initiation of steroid treatment may be life saving in both diseases. Most importantly, steroids should be withdrawn once a complete biochemical remission has been achieved. This may be the only way to discriminate between immune-mediated DILI and true AIH, since the latter usually relapses and develops into a chronic disease. More importantly, unnecessary long term treatment can thus be avoided in most patients with immune-mediated DILI.

Therefore, it seems important to differentiate between AIH with DILI, drug induced AIH, and immune-mediated DILI (with features of AIH) since long term treatment and prognosis may significantly differ.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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