JOURNAL
OF HEPATOLOGY

Drug-induced liver injury due to nitrofurantoin: Similar clinical features, but different HLA risk alleles in an independent cohort

To the Editor:

We read with great interest the recent article on the subject of nitrofurantoin-related drug-induced liver injury (DILI) in the DILIN cohort from Chalasani and colleagues.[1] Independently of the DILIN project, projects entitled DILIGEN and iDILIC, involving both retrospective and prospective recruitment of DILI cases for the study of genetic susceptibility, took place from 2004 to 2014 outside the USA. A total of 26 nitrofurantoin DILI cases from these studies passed expert adjudication and were classified as possible, probable or highly probable based on Roussel Uclaf Causality Assessment Method (RUCAM) causality scores of 3 or higher. These cases were included in a recent genome-wide association study (GWAS) on DILI.[2] The DILIGEN/iDILIC cases were recruited from the United Kingdom (n = 21), Netherlands (n = 3), Australia (n = 1) and South America (n = 1). All had white European ethnicity. Interestingly, the clinical features of this cohort were very similar to those described in the recent report:[1] 85% of cases were female, mean age was 62 years, and hepatocellular injury was observed in 73% of cases. For RUCAM, 70% had a score of 6 or above, which represents probable or highly probable causality. When we divided the cohort based on nitrofurantoin exposure time, 31% had received the drug for <7 days, 31% for 8 to 365 days and 38% for >365 days. This longer exposure group is smaller in our cohort than in the recent DILIN report.[1]

As previously described in detail, HLA genotype can be imputed from GWAS data with a high level of reliability.[3] Imputed HLA genotypes had already been obtained using this approach for all 26 nitrofurantoin cases as part of the larger GWAS.[2] As summarised in Table 1, which shows HLA alleles showing differences between cases and controls with uncorrected *p* values <0.05, certain HLA alleles were more common among the nitrofurantoin DILI cases compared with population controls. The strongest association was with *HLA-A*33:01*, which we reported previously to be a risk factor for DILI due to several drugs, particularly terbinafine.[2] The haplotype *HLA-DRB1*07:01–HLA-DQA1*02:01–HLA-DQB1*02:02*, previously reported by others to be a risk factor for some forms of DILI (*e.g.* due to lapatinib and asparaginase),[4,5] also appears more common in our cohort, but none of our nitrofurantoin DILI cases had exposure to other drugs for which this haplotype association had been reported. None of the cases in our cohort were positive for *DRB1*11:04*, in contrast with the findings of Chalasani *et al.*[1] It is possible that we did not detect this association in our cohort due to a lower incidence of cases with DILI after prolonged nitrofurantoin exposure. However, we did not see a significant increase in frequency of *HLA-A*01:01* in our cohort either (odds ratio 1.29; 95% CI 0.66-2.54; $p = 0.45$), even though this was detected more commonly in patients with short nitrofurantoin exposure in the DILIN cohort.[1]

Even though it is possible to obtain interesting data on genetic risk factors for DILI, especially HLA, using small case cohorts, we believe some caution is needed. In particular, use of replication cohorts is generally recommended in genetic studies.[6] Assembly of a larger cohort of nitrofurantoin DILI cases would be useful both in resolving the issue of at-risk HLA genotypes and in identifying non-HLA genetic risk factors for this serious and relatively common form of DILI.

Table 1. Comparison of imputed HLA allele frequencies in nitrofurantoin DILI cases (n = 26) compared with controls.

Allele	Odds ratio	95% CI	*p* value
*HLA-A*33:01*	10.93	2.447-48.84	0.0017
*HLA-DQB1*02:02*	2.483	1.231-5.01	0.0111
*HLA-A*30:02*	5.563	1.274-24.29	0.0225
*HLA-DQA1*02:01*	2.158	1.106-4.208	0.0240
*HLA-DRB1*07:01*	2.141	1.099-4.171	0.0253
*HLA-DPB1*16:01*	4.836	1.099-21.27	0.0370
*HLA-C*06:02*	2.202	1.047-4.63	0.0373

Frequencies in cases were compared with those in 10,588 controls of European ancestry, as described previously.[2] Only alleles where the difference between cases and controls shows a *p* value <0.05 are listed. Odds ratios and *p* values were calculated by conditional logistic regression as described previously.[2] DILI, drug-induced liver injury.

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Received 22 November 2022; Accepted 23 November 2022; Available online 30 November 2022
https://doi.org/10.1016/j.jhep.2022.11.022

Financial support

This study is part of the COST Action "CA17112 - Prospective European Drug-Induced Liver Injury Network"supported by COST (European Cooperation in Science and Technology) (www.cost.eu). The genome-wide association study and iDILIC case enrolment and sample collection was funded by the International Serious Adverse Events Consortium. The University of Nottingham sample collection was funded by the National Institute for Health Research (NIHR) Nottingham Digestive Diseases Biomedical Research Unit at the Nottingham University Hospitals NHS Trust and University of Nottingham. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. GPA is the gastrointestinal and liver disorder theme lead for the NIHR Nottingham BRC (Reference no: BRC-1215-20003). The Spanish DILI Registry is partly funded by the Spanish Medicine Agency, Fondo Europeo de Desarrollo Regional - FEDER (FIS PI19_00883, PI 21_01248). CIBERehd is funded by Instituto de Salud Carlos III.

Conflicts of interest

Ann K. Daly, Einar S. Bjornsson, M. Isabel Lucena, Raul J Andrade and Guruprasad P. Aithal do not have any conflicts of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

All authors developed and performed the original study. Ann Daly and Guruprasad Aithal wrote the manuscript in consultation with the other authors with all authors editing and approving the final version.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.11.022.

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Screening for NAFLD and its severity in type 2 diabetic patients: Value of magnetic resonance imaging and outstanding issues

To the Editor:

We read Ajmera *et al.*'s original manuscript[1] with great interest. Screening for non-alcoholic fatty liver disease (NAFLD) is indeed crucial in the type 2 diabetes population because of the intricate links between insulin resistance and hepatic steatosis.[2] We were therefore looking forward to prospective studies in this area.[2] The great value of their analysis was the use of MRI-proton density fat fraction (PDFF) and elastography in the vast majority of patients, which allowed for optimal non-invasive assessment of the degree of steatosis and fibrosis[3] and to highlight advanced fibrosis (and even hepatocellular carcinoma) in patients with a low fibrosis-4 (FIB-4) score, for example.[1] Although best suited for easy, large-scale screening, the FIB-4 score should indeed be used with caution in patients with diabetes.[4] However, these results raise additional questions.

First, did the selected patients represent a full sample of patients with type 2 diabetes? Over 7 years, with recruitment in primary care and endocrinology clinics, the authors only screened 524 patients. We therefore wonder whether study participation was proposed to all patients with type 2 diabetes seen during this period who met inclusion criteria.

Secondly, the presence of one of the following criteria compatible with newly diagnosed diabetes was required as inclusion criteria (diabetes symptoms and plasma glucose ≥200 mg/dl or fasting plasma glucose ≥126 mg/dl or plasma glucose ≥200 mg/dl during a 75-g oral glucose tolerance test on two separate tests or HbA1c ≥6.5%). However, in the results section, 72% of patients were already treated with glucose-lowering drug(s). We therefore wonder whether this was a first diagnosis of NAFLD. Indeed, NAFLD is increasingly screened in endocrinology units, internal medicine and primary care, although progress is still needed with regard to screening. The authors provide the rate of diagnosed fibrosis and cancers, but do not mention the proportion of patients in whom NAFLD was likely already diagnosed and followed in hepatology clinic. In other words, it would be interesting to know how many new diagnoses (of NAFLD, cirrhosis and/or HCC) such a large-scale screening intervention would deliver.