When is Suspected Drug Induced Liver Injury (DILI) not DILI?

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Background

The diagnosis of drug induced liver injury (DILI) is difficult as it is a common source of abnormal liver tests and is a diagnosis of exclusion.

To aid in diagnostic decision making, we reviewed cases enrolled in DILIN with an initial diagnosis of DILI that were ultimately adjudicated to have abnormal liver tests due to other causes.

Aims

To describe the clinical characteristics of cases of abnormal liver enzymes, initially presumed to be from DILI, that were eventually ascribed to alternative etiologies.

Methods

DILIN Expert Opinion Process:
All cases are independently assessed by 3 experts participating in the DILIN. One of 5 score categories based on percent likelihoods are assigned by each reviewer (see below). Scores for overall case and individual agents in multi-agent cases are assigned.

DILIN Score-Category & % Likelihood of DILI
1-Definite >95%
2-Very likely 75-95%
3-Probable 50-74%
4-Possible 25-49%
5-Unlikely <25%

From inception in 2004 to April 16, 2009, assessments were done based on data from the enrollment visit only. After April 16, 2009, the protocol was modified so that adjudication was done 6 months after enrollment, thus allowing inclusion of 6-month follow-up data into the assessment process.

Cases that were at least probable (DILI Likelihood Scores 1-3) were compared to cases assessed as unlikely DILI (5). Unlikely cases were further reviewed for salient features and trends over time.

Descriptive data were collected and bivariate comparisons made where appropriate

Results

From 9/04 to 12/21, 1916 cases were adjudicated, 134 (7%) were scored as 5--unlikely DILI.

There were no demographic features to distinguish DILI from unlikely DILI.

Unlikely cases more often had underlying renal disease (18% vs 9%, p=0.005), HIV (7% vs 2% p<0.001), hepatitis C (HCV) (12% vs 3% p<0.001), or hepatitis B (5% vs 1 % p<0.001).

Latency for initially suspect drugs in unlikely cases was either brief (< 1 week 9% vs 5% in likely DILI) or very long (>24 weeks 28% vs 16%) p=0.002 overall.

The most common alternative diagnoses for unlikely cases were autoimmune hepatitis (20%) and HCV (20%) (Table 1).

Among white patients, carriage frequency of two copies of HLA-DQA1*03:01 was greater among those finally assessed as having AIH (13%) compared to DILI cases (3%). (Figure 1)

Patients with unlikely DILI had greater all-cause (16% vs 7%, p<0.001) and liver-related mortality (10% vs 3%, p<0.001). Unlikely DILI cases died within six months at a higher rate (14% vs 6%, p=0.004). Liver transplant rates, hospitalization rates, and duration of acute illness were similar.

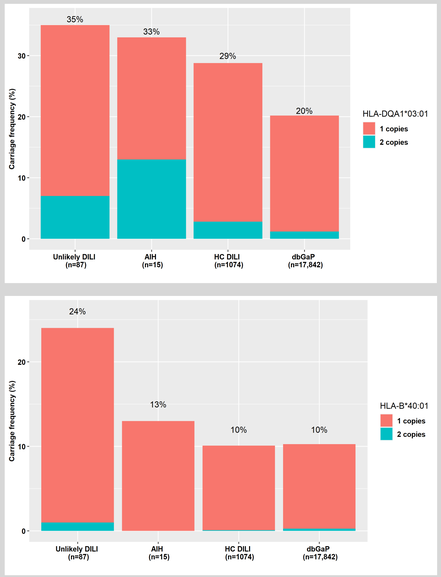

Figure 1: of HLA-DQA1*03:01 and HLA-B*40:01 Carriage rates for unlikely, AIH, DILI cases and the general population

Results (continued)

Table 1: Alternative diagnoses in unlikely DILI cases

Diagnosis	n	%	Comments
Autoimmune hepatitis	27	20.1	• The most common incorrectly implicated class of medications were antibiotics (9/27) followed by Herbal/Dietary Supplements (HDS) (8/27). • Nearly all had liver biopsies, but findings were not diagnostic for DILI or AIH. • Other common themes among these cases were 1) prevalent underlying immune-mediated disease (systemic lupus erythematosus, hypothyroidism, inflammatory bowel disease, etc.) in 8/27 cases; 2) negative or relatively low antinuclear antibody titers (<1:80) which increased on follow up; 3) a response to corticosteroids (CS) in 14/27 with six of these having a flare in enzymes after reduction in dose or withdrawal of CS.
Hepatitis C	27	20.1	• 24 were acute HCV and three chronic. • Of the 24 acute cases, 17 were enrolled prior to 2011 and none since 2017. Most of these cases had negative HCV antibodies and were discovered to have a positive HCV viral load later in their clinical course. • Three patients had prevalent detectable HCV virus which later cleared on follow up.
Gallstone/biliary obstruction	18	13.4	• Eight cases had biliary tract malignancies. • Three cases had primary sclerosing cholangitis. • Normal imaging in some patients who acutely had passed a stone. • No differences in the presence of stones (3.3% vs. 6.7%, p=0.32), or ductal dilation (3.3% vs. 2.5%, p=0.89) between unlikely DILI and DILI cases.
Hepatitis E	11	8.2	• Diagnosis often delayed as test for HEV is a send-out in most centers.
Sepsis	7	5.2	• Frequently in Intensive Care Unit on multiple drugs and hypotensive.
Other (>20 diverse etiologies)	44	32.8	• Etiologies included alcohol, myopathy, Epstein Barr virus, cytomegalovirus, nonalcoholic steatohepatitis, metastatic cancer, and granulomatous liver disease.

Summary

DILI is often difficult to diagnose, even among experienced hepatologists.

Demographic factors do not appear to be helpful in the initial differentiation of DILI vs unlikely DILI.

Very short or very long latency between suspect drug and initial liver injury decreases likelihood of true DILI.

AIH and HCV are frequent alternative diagnoses.

Genetic testing in white patients where AIH vs DILI is being considered might be helpful.

Conclusion

Longitudinal follow up of patients with presumed drug induced liver injury is essential to reexamine and refine the likely diagnosis, treat an alternative disease, and potentially absolve a medication presumed to have caused drug induced liver injury.