Ezetimibe-Related Drug Induced Liver Injury: An Uncommon Offender

Anthony P. Nguyen MD, Eyerusalem Akpan MD, Yiting Li MD, Christopher Chang MD, PhD
Department of Gastroenterology & Hepatology, University of New Mexico Health Sciences Center, Albuquerque, New Mexico
Department of Gastroenterology & Hepatology, Raymond G. Murphy VA Medical Center, Albuquerque, New Mexico

Introduction

- Drug Induced Liver Injury (DILI) occurs due to hepatic exposure to a synthetic or naturally occurring compound.
- DILI can be divided into two subtypes based on different pathophysiologic mechanisms: intrinsic and idiosyncratic
- Ezetimibe is a commonly prescribed 2nd line agent for achieving reduction of LDL levels in patients with hyperlipidemia and can lead to an idiosyncratic DILI
- In rare cases, idiosyncratic DILI can cause seropositivity and act as a mimic to autoimmune hepatitis

Case Presentation

A 67 year-old man with a history of Hashimoto's thyroiditis presented with abdominal pain, "dark" urine, and fatigue.

Clinical Course:
HPI: Admitted for abdominal pain, dark urine and fatigue. Prior to admission he had been out hunting and had a stable medication regimen aside from recently starting ezetimibe 6 weeks prior.

Vitals/Physical Exam:
- Afebrile, hemodynamically stable, no vital sign abnormalities
- Exam with mild tenderness to palpation in RUQ

Lab Values:
- Initial liver function tests (LFT) were significantly elevated compared to baseline
- Urinalysis negative for blood or bacterial byproducts.
- Full diagnostic work-up obtained and were negative such as:
  - Chronic liver disease (ceruloplasmin, iron panel, ETOH level, lipid panel)
  - Infectious causes (Hep A, B, C, D, E, EBV, CMV, HSV)
  - Autoimmune serologies can be seen in Table 3.

Imaging:
- RUQ Ultrasound: Negative for hepatic lesions, intrahepatic biliary dilation, or cholelithiasis. Portal, hepatic and splenic veins are patent.
- CT Abdomen: Mildly nodular liver without enlargement, no intrahepatic ductal dilatation, no pancreatic abnormalities

Figures

Types of Drug-Induced Liver Injury (DILI)

	Intrinsic	Idiosyncratic
Time of Onset	Immediate	Delayed (Latency Period)
Reproducible?	Yes	No
Dose-Responsive?	Yes	No

Liver Function Tests

	Baseline	On Admission	1 Week Post-Discharge	2 months Post-Discharge
AST	43	2159	712	37
ALT	34	3011	1228	29
Alkaline Phosphatase	93	245	240	97
Total Bilirubin	1.3	2.7	2.1	1.1
Total Protein	7.6	7.6	7.0	8.0
Albumin	4..3	3.5	3.5	4.4

Autoimmune Serologies (on admission)

ANA	ASMA	IgA	IgG	IgM
1:320 (elevated)	1:320 (elevated)	109	516	56

Hospital Course Overview:
- Admitted for abdominal pain, dark urine and malaise and found to have significant LFT elevations with elevated autoimmune serologies in the setting of recent initiation of ezetimibe therapy.
- Full diagnostic work-up mostly unremarkable aside from elevated autoimmune serologies (see table above).
- RUCAM score of 10 indicated "highly probable" causal relationship between ezetimibe and liver injury.
- LFTs improved prior to discharge and had returned to baseline at subsequent hepatology clinic visits.

Discussion

- Ezetimibe is a less common cause of idiosyncratic DILI with ~4 other cases in the literature.
- Idiosyncratic DILI is often asymptomatic and has a delay between toxin exposure and onset of liver injury (latency period).
- The liver plays an important immunologic role and this makes it susceptible to developing autoimmunity via a hapten-like effect.
- Seropositive idiosyncratic DILI can mimic autoimmune hepatitis.
- Removal of the suspected offending agent with improvement of LFTs is one method of distinguishing between DILI and autoimmune hepatitis

Learning Points

- Ezetimibe is a less common offender in cases of DILI and is a commonly prescribed lipid lowering medication for patients that are refractory to statin therapy.
- DILI can cause an autoimmune-like hepatitis that is difficult to distinguish from true primary autoimmune hepatitis.
- Current guidelines recommend against serial LFT monitoring for patients on statin therapy but obtaining LFTs during the latency period could be clinically useful if incidence of ezetimibe related DILI were to increase.

References

Fan, J. H., Liu, G. F., Lv, X. D., Zeng, R. Z., Zhan, L. L., & Lv, X. P. (2021). Pathogenesis of autoimmune hepatitis. *World Journal of Hepatology*, *13*(8), 879. https://doi.org/10.4254/WJH.V13.I8.879
Fontana, R. J. (2014). Pathogenesis of idiosyncratic drug-induced liver injury and clinical perspectives. *Gastroenterology*, *146*(4), 914–928. https://doi.org/10.1053/j.gastro.2013.12.032
Fontana, R. J., Watkins, P. B., Bonkovsky, H. L., Chalasani, N., Davern, T., Serrano, J., Rochon, J., & DILIN Study Group. (2009). Drug-Induced Liver Injury Network (DILIN) prospective study: rationale, design and conduct. *Drug Safety*, *32*(1), 55–68. https://doi.org/10.2165/00002018-200932010-00005
Zhou, Z., Xu, M.-J., & Gao, B. (2016). Hepatocytes: a key cell type for innate immunity. *Cellular & Molecular Immunology*, *13*(3), 301–315. https://doi.org/10.1038/cmi.2015.97
Czaja, A. J. (2011). Drug-Induced Autoimmune-Like Hepatitis. *Digestive Diseases and Sciences*, *56*(4), 958–976. https://doi.org/10.1007/s10620-011-1611-4