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Biosketch

Dr. Fontana is a translational investigator with research interests in drug induced liver injury and acute liver failure. Dr. Fontana completed his gastroenterology/hepatology training at the University of Michigan and has been on the faculty since 1995. He is currently a Professor of Medicine and Medical Director of Liver Transplantation. He is a principal investigator at one of the 6 Drug Induced Liver Injury Network (DILIN) clinical sites and also serves as Co-chair of the DILIN Steering committee. He has helped lead efforts to carefully phenotype patients with DILI as well as determine the likelihood of early adverse outcomes and chronicity with prolonged follow-up in the DILIN prospective study. Dr. Fontana is also the current Chair of the AASLD Hepatotoxicity Special Interest Group. He has also been an active member of the US Acute Liver Failure Study Group as a site principal investigator and lead investigator on the long-term outcomes protocol since 1998.

Abstract: 2017 I-4: Chronic liver disease after acute hepatocellular DILI

Incidence of chronic DILI

The Drug Induced Liver Injury Network (DILIN) Prospective study has reported that ~60% of patients with bona fide DILI in the US required hospitalization and that 10% died or underwent liver transplantation within 6 months of DILI onset. Furthermore, 19% had liver injury 6 months after DILI onset defined by an elevated liver biochemistry level, abnormal liver imaging or histopathology. Amongst 660 adult patients with bona fide DILI, African-American race, higher alk phos levels at presentation and pre-existing heart disease/malignancy were independent predictors of chronicity. Whether these patients will develop clinically significant liver disease or simply experience slowly resolving liver injury during prolonged follow-up remains uncertain. Prior studies have suggested that continued administration of the suspect drug and presentation with an acute cholestatic liver injury profile may result in a slower rate of laboratory improvement and an increased risk of developing chronic liver disease. However, the number of patients reported in these studies was limited and varying criteria were used to define chronic liver injury. Recently, the 2 year outcomes of 99 consecutive adult DILI patients enrolled in the DILIN prospective study with ongoing liver injury 6 months after DILI onset were reported. In this study, patients with persistent liver injury (“persisters”) were defined by a serum AST or ALT > 1.5 x upper limit of normal (ULN) or an alkaline phosphatase > ULN at 12 months after DILI onset. Those not
meeting these criteria were considered to have minimal to resolved liver injury (resolvers). Using this definition, nearly 75% of the cohort had laboratory evidence of ongoing liver injury at 12 months after DILI onset while the remaining 25% had resolved their liver injury with normalization of laboratory results. Of note, the majority of subjects were not jaundiced at month 6 and this proportion remained low during follow-up.

**Predictors of persistence**

Using logistic regression, the mean duration of suspect medication use in the 113 patients was significantly longer than the 485 patients with self-limited DILI. However, gender, BMI, immunoallergic features (i.e. eosinophilia, rash, fever) and autoantibodies at DILI onset were not associated with persistent liver injury. However, older patient age and higher serum alkaline phosphatase levels at presentation were both significant and independent risk factors for persistent DILI. The observed association of persistent liver injury with increasing patient age is not surprising. Studies of ALF patients have demonstrated that older subjects are more likely to die or experience greater morbidity presumably due to impaired hepatic regeneration. Older age is also a strong determinant of developing chronic HCV after initial exposure and older patients demonstrate greater evidence of hepatic inflammation and fibrosis progression during follow-up. Aging also promotes the development of hepatic inflammation and liver cell injury in animal models of hepatic steatosis. Subjects with cholestatic liver injury at DILI onset were at greater risk of having persistent liver injury during prolonged follow-up. Prior reports have demonstrated that individual drugs associated with cholestatic liver injury early on can lead to severe prolonged cholestasis and even ductopenia during follow-up. In particular, some patients with severe acute cholestatic drug reactions may go on to develop protracted liver disease with repeated hospitalizations and even development of cirrhosis. Furthermore, subjects with a cholestatic DILI episode in one study were more likely to develop chronic liver injury and a small proportion of these patients also developed progressive liver fibrosis. The 17 patients with clinically driven follow-up liver biopsies in the DILIN study provided a unique opportunity to explore the pathological evolution of chronic liver injury from DILI. The biopsies mainly showed chronic injury patterns with varying severity of hepatic fibrosis and just over half showed chronic cholestasis. This histological pattern of injury is in keeping with the persistent cholestatic laboratory injury profile and is unlikely to be the result of pre-existing liver disease. In patients with a baseline and a follow-up biopsy, fibrosis progression was seen in two-thirds of cases, even though the time between biopsies was relatively short. Interestingly, all six patients with duct loss on follow-up did not have evidence of early duct loss on their initial biopsy but had a mixed or cholestatic lab profile at initial presentation and at the time of follow-up biopsy. In addition, all 6 of these patients with ductopenia during follow-up also had fibrosis progression.

**Summary/ conclusions**

Prospective registry studies have demonstrated that 5 to 10% of patients will die or undergo liver transplantation within 6 months of DILI onset. Patients with severe acute hepatocellular injury are more likely to suffer untoward consequences but subjects with severe mixed/cholestatic reactions may also not do well. At 6 months after DILI onset, the frequency of ongoing liver injury varies between 10 to 20% depending upon the criteria used to define chronicity. The DILIN prospective study showed that 75% of those with liver injury at 6 months after DILI onset have residual liver disease at month 12. Although lab abnormalities generally improved over time, some patients experienced rapid fibrosis progression. In addition, a recent case series from DILIN demonstrated that 26 of 363 enrolled patients with an evaluable liver biopsy had evidence of bile duct loss during follow-up. Whether or not steroids, choleretic agents, or antioxidants may favorably impact the rate of disease progression is unknown but worthy of study in a prospective clinical trial.

*References on request to author.*