Reply to "Biliary atresia: Does ethnicity matter?"

To the Editor:

We welcome the comment of Girard *et al.* [1] to our systematic review on the epidemiology of primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC) [2]. The authors underscore the need for proper assessment of ethnicity in epidemiological studies of rare diseases such as biliary atresia, PSC, and PBC. The apparent familial risk, albeit with a low absolute risk, together with the reported genetic risk loci, point in the direction of a complex genetic predisposition belying both PSC and PBC. Recently, disparate associations with several genetic risk loci have been reported in PSC patients from various ethnic backgrounds [3]. For PBC, little is known about ethnic differences since the majority of studies have been performed with Caucasian patients. Notably, a large multicenter study in the US was performed comparing PBC patients with geographically and ethnically diverse backgrounds [4]. The authors showed more severe disease in African Americans and Hispanics compared to Caucasians. In addition, for inflammatory bowel disease, which is closely associated with PSC, it has been well documented that incidence rates in 2nd generation immigrants with a different ethnic background assume the same levels as those for the indigenous population, pointing towards environmental factors [5–7]. For PSC, population-based trends in incidence and prevalence rates with regard to ethnic background are lacking. One study from Southern Israel reported higher prevalence rates for PBC among Jews and immigrants compared to Arabs and native Israelis and in a study from Southeast Asia, the prevalence rate in the Chinese population was almost twice as high as in the Malay population, though the small number of included patients is a limitation of both studies. [8,9] The data presented by Girard *et al.* [1] exemplify our conclusion that large true population-based epidemiological studies with meticulous case-finding, case-ascertainment, as well as detailed phenotyping (including ancestry) are needed to provide clues for unraveling genetic and environmental risk factors for these diseases.

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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Statin hepatotoxicity and the dilemma of causality in rare hepatic adverse drug reactions

To the Editor:

In his editorial, Bader [1] highlights the problems associated with assessing statin-induced hepatotoxicity, a rare hepatic adverse drug reaction (ADR). However, the definitions of hepatotoxicity and idiosyncratic reactions are used by Bader in a confusing way. With the appraisal "Yes! Statins can be given to liver patients" Bader also creates the impression that statins are withheld from patients with liver disease [1]. At least outside the US, however, mainstream physicians including hepatologists never had a problem prescribing statins to their liver patients; uncertainty exists only how to proceed in cases of decompensated liver cirrhosis.

Björnsson *et al.* [2] have clearly shown that statins can cause idiosyncratic hepatotoxicity. In general, drug hepatotoxicity refers to either of two different underlying reactions, namely the dose dependent, predictable, and hence intrinsic reaction, or the dose independent, unpredictable, and hence idiosyncratic one. Limiting "hepatotoxicity" to the dose dependent reaction leaves the reader with the impression that statins are not hepatotoxic due to lack of dose dependency [1]; on the contrary, statin

metabolism is reduced in patients with preexisting liver disease and statins are known to increase ALT [3,4], with a slight dose dependency of ALT increase for higher statin doses ([4], Table 3).

At no time did Björnsson *et al.* [2] claim a dose dependent statin hepatotoxicity, but described a rare, severe idiosyncratic statin hepatotoxicity; reexposure with similar symptoms nearly proves a causal relationship. Bader should have withdrawn his previous statement concerning the myth of statin hepatotoxicity [5], because this proposal was incorrect and misleading; considering the very low incidence in clinical studies, spontaneous reports, and case reports, the decision still will result in prescribing statins rather than withholding them.

Most systems to detect rare ADRs rely upon active reporting systems where cases are only included if physicians suspect a causal relationship. These systems are heavily biased toward assuming causality even if this does not exist; the dilemma of prejudice and selective data reporting, as is prevalent for other cases of potential hepatotoxicity by drugs and herbs, was elegantly solved by Björnsson *et al.* using the diagnostic algorithm of CIOMS, also called RUCAM [2]. Despite its known shortcomings, this causality assessment method has been used extensively to evaluate hepatotoxicity by drugs [6]. In relation to the study on statin hepatotoxicity by Björnsson *et al.* [2], the applied method of CIOMS/RUCAM was considered the best method available for this inquiry [1].

Björnsson *et al.* [2] identified cases of idiosyncratic hepatotoxicity due to statins and discussed their results regarding previous reports on other cases of statin hepatotoxicity. This confirms that package inserts of warnings about the rare hepatotoxicity problem should remain, as opposed to the viewpoint of Bader who prefers its deletion [5]. The cautionary statement is valuable information for physicians and patients and a preventive measure for legal consequences that otherwise may reach statin manufacturers in cases of statin hepatotoxicity.

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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Reply to: "Statin hepatotoxicity and the dilemma of causality in rare hepatic adverse drug reactions"

To the Editor:

ALT monitoring for statins no longer recommended

It is gratifying that since the publication of my editorial review on statins and the liver (February 2012 issue of the *Journal*), the USA Food and Drug Administration (FDA) announced on 28 February 2012, a marked relaxation of package insert language on all statins [1]. Since pharmaceutical safety boards of many countries closely follow the insert language of the FDA, these revisions will be of interest to a worldwide audience.

What was previously a hodge-podge of comments about the liver that differed for each statin, the discussion has been greatly redacted and made uniform. Briefly, the statin labels no longer recommend ALT monitoring after starting a statin. Should acute liver disease develop, the statin should be withheld until the cause is ascertained. This would imply that the patient should be told before treatment about possible signs of drug-induced liver injury and urged to inform the physician if these symptoms occur. The label reminds the reader that an ALT elevation can also occur from muscle injury.

These changes represent a seismic shift in policy. The FDA clearly agrees that an elevated ALT after initiating a statin is not a sign of hepatotoxicity. Instead, the shift in monitoring for symptoms follows the same successful approach as for isoniazid monitoring. I have advocated these changes for some time [2–4].

Still, the labels advise that liver tests be checked prior to initiating a statin, and that statins should not be given to patients with "active liver disease." The phrase "active liver disease" is not defined on the label nor anywhere else I am aware of.

The correspondents and I both agree that statins can be given to patients with chronic liver disease. There is reasonable disagreement over use in decompensated liver patients simply due to a lack of data. However, data are starting to appear. In Spain, Abraldes *et al.* gave 40 mg of simvastatin or placebo to 60 cirrhotics with portal hypertension (proved by WHVP) in a randomized