ANNALS of Hepatology

LIVER NEWS ELSEWHERE

May-June, Vol. 11 No.3, 2012: 418-420

Hepatotoxicity associated with statins

Rolf Teschke*

* Department of Internal Medicine II, Division of Gastroenterology and Hepatology, Klinikum Hanau, Academic Teaching Hospital of the Medical Faculty of the Goethe University Frankfurt/Main, Germany.

Article commented

Björnsson E, Jacobsen EI, Kalaitzakis E. Hepatotoxicity associated with statins: Reports of idiosyncratic liver injury post-marketing. *J Hepatol* 2012; 56: 374-80.

Comments

In their study, Björnsson *et al.*[1] evaluated the question whether and to what extent drug-induced liver injury (DILI) may be associated with the use of statins, a life-reserving therapy in numerous patients with cardiovascular diseases associated with hypercholesterolemia. The authors analyzed reports on overall adverse reactions suspected to be due to statins received by the Swedish Adverse Drug Reactions Advisory Committee (SADRAC) during 1988-2010. The most common types of suspected adverse drug reactions (ADRs) were DILI in 124/217 cases and rhabdomyolysis/myalgia in 42/217 cases.[1] The latter condition is in line with the known and reported musculoskeletal pains.[2] Considering these 124 cases with primarily suspected statin hepatotoxicity in a further analysis, 25 cases had to be excluded due to mild elevations of liver tests and 26 cases due to unlikely relationship and/or lack of data; in the remaining 73 cases, the causal relationship for statins was at least possible. The authors conclude that idiosyncratic liver injury may be associated with the use of statins, but this reaction was considered rare.

Correspondence and reprint request: Rolf Teschke, M.D.
Professor of Medicine. Department of Internal Medicine II
Klinikum Hanau.
Academic Teaching Hospital of the Goethe University of Frankfurt/Main
Leimenstrasse 20. D-63450 Hanau, Germany
Tel.: +49-6181/21859. Fax: +49-6181/2964211
E mail: rolf.teschke@gmx.de

Manuscript received: February 16,2012.
Manuscript accepted: February 17, 2012.

In the past, there was some uncertainty regarding the hepatotoxic potency of statins, and the existence of statin hepatotoxicity has been questioned and labelled as myth.[3] However, the thorough analysis of Björnsson et al.[1] clearly substantiates the existence of rare statin hepatotoxicity as a fact rather than a fiction and contradicts previous statements to the contrary.[3] In particular, statin hepatotoxicity was found in a total of 21 patients with a probable and highly probable causality for statins in 14 and 7 cases, respectively.[1] Among the 7 patients with a highly probable causality for statins, there were 3 cases with a confirmed positive rechallenge test, providing additional support for the existence of statin hepatotoxicity. Of note, the definition of hepatotoxicity was strict and conservative, because only cases with > 5 x upper limit of normal (ULN) in aminotransferases and/or > 2 x ULN in alkaline phosphatase were included in their study. This approach certainly reduces a priori false positive signals such as concomitant NAFLD or chronic liver diseases, and it substantially ascertains the conclusions presented by the authors.[1]

With the scale of CIOMS (Council for International Organizations of Medical Sciences) as the best and most commonly used method to assess hepatotoxicity cases in assumed relation to synthetic drugs and herbs,[4-11] this well founded causality assessment method with its discussed few and minor shortcomings was employed and adequately evaluated in the present study.[1] Limitations of the CIOMS scale were discussed also earlier[6,12-18] and led to corresponding updated versions to improve the quality of assessment.[12,16-18] The present analysis was of retrospective nature and did not consider infections by herpes simplex virus, varicella zoster virus, and hepatitis E virus,[1] as recommended by others.[16-20] These infections and other alternative diagnoses were diagnosed in various hepatotoxicity studies,[9,19,20] calling for a skilful consideration of differential diagnoses.[18] SADRAC as the reporting portal for the current Swedish cases had obviously problems with completeness of some case

data,[1] a feature common also to other regulatory portals.[7-10,21,22] They rely primarily on their passive rather than an active adverse event reporting systems to identify drug and herb safety problems including DILI and herb induced liver injury (HILI). These shortcomings call for respective regulatory improvements.

There is some uncertainty around the 52 patients with liver disease in a relationship to statins at an only possible causality level.[1] This raises the principal issue whether this particular group of cases should be included in or excluded from the general characterization of statin hepatotoxicity. Confounding variables may include comedication, preexisting disorders including liver diseases, or poor data quality. Problems may also emerge when these 52 patients are used for calculation of the incidence of HILI associated with the use of statins.

In their excellent study, the authors present a balanced view and conclude that DILI can occur in patients on statins, but this should not discourage people to use statins.[1] Considering that these reactions are extremely rare, they emphasize that it is hardly cost-effective to perform liver tests in patients on statins and that their results do not answer the question whether or not monitoring is reasonable. Their recommendations include the proposal that measurements of liver tests should as always be based on the clinical scenario and suspicion of a liver disease.

As opposed to the intrinsic form of hepatotoxicity, which is predictable and dose dependent and shows a short and consistent latency period, high incidence among users, and experimental reproducibility,[23] the reported cases of statin hepatotoxicity clearly represent the idiosyncratic form of hepatotoxicity.[1] This idiosyncratic form of hepatotoxicity occurs with a low incidence in users at normal doses and is characterized by its long and variable latency period, unpredictability, dose independency including lack of daily overdose, and lack of reproducibility in experimental animals.[23] For subclassification of the idiosyncratic hepatotoxicity, the immunologic and the metabolic subtype have to be distinguished. The immunologic subtype appears unlikely to apply to statin hepatotoxicity since prerequisites such as short duration of exposure of 1-5 weeks, features of overt hypersensitivity, and prompt response to reexposure with 1-2 doses[23] are not apparent in the reported cases.[1] However, the metabolic subtype exhibits various characteristics suggestive for cases of statin hepatotoxicity.[23] Among these items are a variable duration of exposure of one week up to 12 months, the absence of clinical features of hypersensitivity such as rash, fever, and eosinophilia, and the delayed response to rechallenge of many days or weeks. Presumably, a weak dose dependency in a few susceptible humans who adhere to recommended doses may be present in the assessed cases, another facultative criterion of the metabolic subtype. Overall assessment therefore suggests that statin hepatotoxicity is best described as the metabolic subtype of the idiosyncratic form of hepatotoxicity, based on a reaction of some sort of metabolic aberration in a few unusually susceptible humans.

Special attention merits the somewhat awkward editorial commentary of Bader,[3] which relates to both the original report of Björnsson *et al.*[1] and his own statements, published under the title *The myth of statin-induced hepatotoxicity* in a previous report.[24] Here Bader originally refused the existence of statin hepatotoxicity and called for a deletion of the packing inserts, which contain warnings about the problem of hepatotoxicity.[24] By contrast, in his present editorial commentary, Bader now seems to support, at least in part, the well founded conclusions communicated by Björnsson *et al.*[1] and acknowledges that statins are at risk causing rare idiosyncratic hepatotoxicity.[3] To arrive at this statement, however, he surprisingly initiated a semantic discussion, creating confusion through inconsistencies, trying to justify ex post his previous statement of the proposed non-existence of statin hepatotoxicity, and detracting from own misconceptions.[3] Moreover, the title *Yes! Statins can be given to liver patients* and the related comments of the editorial commentary[3] have nothing to do with the report of Björnsson *et al.*[1] but may be seen in context with Bader's share of a utility patent for the possible use of statins in hepatitis B and C.[24]

In conclusion, the sophisticated study of Björnsson *et al.*[1] provides clear supportive evidence for the existence of statin hepatotoxicity and presents a balanced discussion of this clinically important topic, whereas the associated editorial comments remain debated.

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