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Questioning latency period in causality assessment: On the hepatotoxicity of atorvastatin

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Keywords: Hepatotoxicity. Statins. Atorvastatin. Latency period. Causality. Drug-induced liver injury.

Abstract: Atorvastatin is a potent lipid-lowering agent whose potential hepatotoxicity, anecdotally delayed, has been well documented. We present a case of cholestatic hepatitis due to atorvastatin with an unusually prolonged latency period, classically counterintuitive from a causality standpoint.

Dear Editor,

Statins are widely used lipid-lowering agents with proven efficacy in the prevention of cardiovascular events, and their overall risk-benefit ratio is considered highly favorable. Nevertheless, they are a well-recognized cause of hepatotoxicity, with atorvastatin playing a particularly prominent role (1).

We report the case of a 67-year-old male with metabolic syndrome, undergoing continuous daily treatment with 40 mg of atorvastatin prescribed as secondary prophylaxis for cerebrovascular disease. He had been on the medication for 21 months. The patient was admitted with jaundice, without other signs of hepatic insufficiency. Alternative etiologies (infectious, obstructive, and vascular) were

thoroughly ruled out, and atorvastatin was initially continued. Liver biopsy revealed nonspecific cholestatic hepatitis, consistent with a persistent cholestatic pattern of liver injury. Upon delayed discontinuation of the drug, gradual clinical and biochemical improvement was observed (Fig. 1). A CIOMS/RUCAM score of seven indicated probable drug-induced hepatotoxicity.

The temporal relationship between drug initiation and symptom onset is a critical factor in assessing hepatotoxicity. In cholestatic patterns, a latency period exceeding 90 days typically weakens the case for causality. However, several case series have examined the most frequent clinical phenotypes of statin-induced liver injury (1–3), occasionally describing markedly prolonged latency periods, particularly with atorvastatin (4). In fact, in an unpublished update of the National Hepatotoxicity Registry, latency periods exceeding two years were observed in two of 21 atorvastatin-attributed cases. Although seemingly contradictory, this represents a notable exception to the general rule and should be recognized in the complex process of causality assessment. In our case, discontinuation of the drug was delayed for several weeks after biochemical abnormalities appeared, precisely due to the perceived implausibility of a causal relationship. It has been hypothesized that recent dose escalation may underlie some cases of severe, delayed idiosyncratic hepatotoxicity associated with atorvastatin (5).

In conclusion, unusually prolonged latency periods should not exclude the possibility of atorvastatin-induced hepatotoxicity in the appropriate clinical context. Detailed phenotypic characterization of these delayed (and occasionally severe) cases contributes to knowledge and, ultimately, enhances patient safety.

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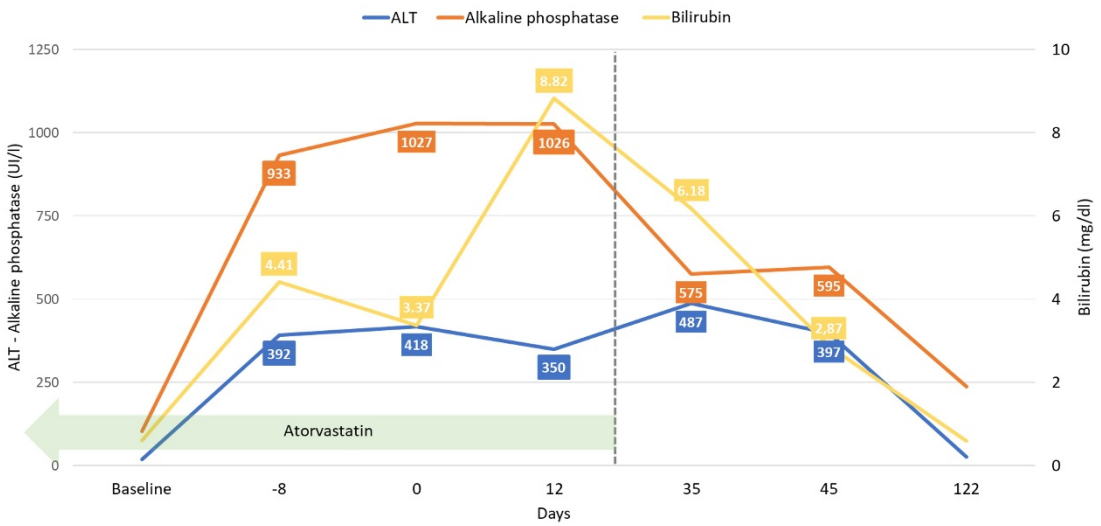

Figure 1. Laboratory progression and its chronological association with atorvastatin. Day 0 marks the initial clinical encounter with the patient. The vertical dashed line indicates the discontinuation of the drug (day 20) following its prior continuous use (horizontal arrow), which had continued for four weeks after the initial biochemical abnormalities were detected. ALT: alanine aminotransferase.