J Korean Med Sci. 2022 Aug 22;37(33):e261
https://doi.org/10.3346/jkms.2022.37.e261
eISSN 1598-6357·pISSN 1011-8934

JKMS

Editorial
Neuroscience

Are Angiotensin II Receptor Blockers Really Safe From Aminotransferase Elevation or Drug-Induced Liver Injury?

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▸ See the article "Incidence and Pattern of Aminotransferase Elevation During Anti-Hypertensive Therapy With Angiotensin-II Receptor Blockers" in volume 37, number 33, e255.

Received: Aug 11, 2022
Accepted: Aug 12, 2022
Published online: Aug 16, 2022

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Disclosure
The author has no potential conflicts of interest to disclose.

Drug-induced liver injury (DILI) is an important but rare adverse event that can assume various forms ranging from mild liver enzyme elevations to death from liver failure. Many commonly used medications as well as herbal and dietary supplements can cause DILI. DILI is also a major cause of drug development discontinuation and withdrawal.[1] According to population-based studies in France and Iceland, the annual incidence of DILI was reportedly 13.9 and 19.1 per 100,000 inhabitants, respectively.[2,3] Angiotensin II receptor blockers (ARBs) are among the most effective and safe antihypertensive agents. In particular, ARBs reduce cardiovascular mortality and protect the kidneys; hence, they are widely used in clinical practice.[4]

In the current issue of the *Journal of Korean Medical Science*, Choi et al.[5] reported the incidence and pattern of aminotransferase elevation during antihypertensive therapy with ARBs. In this retrospective study, significant alanine transaminase (ALT) elevation (ALT > 120 IU/L) and severe ALT elevation (ALT > 200 IU/L) among patients treated with either fimasartan, candesartan, valsartan, or losartan occurred in about 2% and 0.6% of patients, respectively. Among these patients, the probability of ARB-related liver injury was 0.07%. On a multivariable analysis, among the four ARBs, fimasartan was independently associated with a higher risk (hazard ratio, 1.9; 95% confidence interval, 1.39–2.59) of significant ALT elevation, while younger age and elevated baseline ALT levels were independent predictors of significant ALT elevation. In addition, the ALT elevation risk was 1.62 times higher in patients with high serum triglyceride (TG) levels (≥ 150 mg/dL) than in patients with normal TG levels. Only a few ARB-related DILI case reports have been reported to date, and there have been no reports on the incidence of ARB-related DILI. Therefore, this study provides critical information for clinicians.

However, it also has some limitations. First, the Roussel-Uclaf Causality Assessment Method, which was used to diagnose DILI, has limited usefulness in retrospective studies. It is difficult to accurately determine the cause of DILI if the medical records do not accurately describe the history of drinking or taking other medications or herbal medications. Therefore, the incidence of ALT elevation and the probability of ARB-related liver injury might have been overestimated. In addition, there is no mention of drugs other than metformin and statins that can increase ALT elevation. In addition, whether ALT decreases by more than 50% within a certain period after drug discontinuation, which is believed to be the cause, has not been evaluated. Second, there was no accurate record of alcohol

consumption, which often affects liver function tests. Third, there is a lack of analysis of risk factors such as obesity and the presence of non-alcoholic fatty liver disease (NAFLD), which has been increasing in recent years. In particular, the fact that the TG level of patients is an independent risk factor for the occurrence of significant ALT elevation in the multivariate analysis may be due to factors like body weight change, a leading cause of NAFLD that may affect ALT elevation. Finally, in this study, only hepatocellular injury was evaluated among the DILI types, while mixed or cholestatic injury was not evaluated.

Despite these limitations, this study is the first to report the incidence and risk factors of ALT elevation and probable ARB-related liver injury in a relatively large number of patients. According to its results, ARBs are safe, and fimasartan, which has a different metabolic pathway, carries a higher risk of ALT elevation than that of other ARBs. A future prospective cohort study is needed to obtain accurate information on the frequency, clinical characteristics, diagnosis, and treatment of DILI.

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https://doi.org/10.3346/jkms.2022.37.e261