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EDITORIAL

ACE inhibitors: The secret to prevent cirrhosis complications and HCC in NAFLD?

NAFLD, and its progressive form NASH, is currently the leading cause of chronic liver disease worldwide, accounting for an alarming increase in prevalence of cirrhosis, HCC, hepatic decompensation, and need for liver transplantation.[1] Risk factors for acquisition and progression of NAFLD/NASH include features of metabolic syndrome such as diabetes mellitus, cardiovascular disease, and hypertension. The Eight Joint National Committee advises on the use of use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) as first-line drugs for the management of hypertension and lend to cardiovascular protection in vulnerable populations.[2] In a recent retrospective cohort study of 12,327 adult patients with NAFLD, Zhang et al.[3] reported that ACEI treatment was associated with a lower risk of liver-related events (weighted subdistribution HR [sHR], 0.48; 95% CI, 0.35–0.66; $p < 0.001$), HCC (weighted sHR, 0.46; 95% CI, 0.28–0.75; $p = 0.002$), and cirrhosis complications (weighted sHR, 0.42; 95% CI, 0.27–0.66; $p < 0.001$). Such reduction in liver-related events was also notable with patients without chronic kidney disease (CKD) than in those without CKD (CKD-weighted sHR, 0.74; 95% CI, 0.52–0.96; $p = 0.036$; non-CKD-weighted SHR, 0.15; 95% CI, 0.07–0.33; $p < 0.001$).[3] These very compelling results beg the question as to whether use of ACEI, a usual treatment for hypertension and cardiovascular disease, should broadly be used as a repurposed drug for the treatment of NAFLD/NASH.

ACEIs and ARBs, collectively called renin-angiotensin system inhibitors, inhibit vasoconstriction and sodium retention, leading to blood pressure control. Inhibition of the renin-angiotensin aldosterone system (RAAS) has been demonstrated to reduce fibrogenesis in various organs, including the liver. The local RAAS has been implicated in multiple functions including cell growth, differentiation, proliferation and apoptosis, reactive oxygen species generation, tissue inflammation, fibrogenesis, and hormonal secretion.[4] Several studies in a variety of established animal models of hepatic fibrosis support the role of RAAS in liver fibrosis and the antifibrotic effects of RAAS inhibition. Treatment with ACEIs and ARBs in these models attenuated steatosis and prevented the development of lobular inflammation and hepatic fibrosis. These effects appear to be due to the attenuation of oxidative stress and HSC activation, the down-regulation of pro-inflammatory and profibrotic cytokines, suppression of growth factors and TIMP-1, increase in circulating adiponectin levels, and reduction of macrophage infiltration (Figure 1).[5–7] ACEIs and ARBs are also important candidates for cancer chemoprevention. Possible mechanisms for their cancer chemoprevention effects include anti-inflammatory and immunomodulatory (NF-κB inhibition), anti-angiogenic, and anti-fibrotic activities,[8] most of which are also key pathways in the pathogenesis of NASH, fibrosis, and cirrhosis (Figure 1). In animal models, RAAS inhibitors reduced the HCC tumor burden and progression to higher grades of fibrosis, led to regression of HCC, and restored liver histology.[5]

The effect of ACEIs and ARBs in humans is limited, yet provocative. In a cross-sectional study of patients with biopsy-proven NAFLD, the use of ACEIs or ARBs for treatment of hypertension had a negative association with hepatic fibrosis (OR, 0.37; 95% CI, 0.21–0.65; $p = 0.001$).[9] Small pilot studies of ACEIs and ARBs have demonstrated improvement in liver aminotransferases, insulin resistance, and the histologic features NASH.[10,11] In a large cohort ($n = 50,695$) of patients with diabetes and NAFLD, the use of insulin increased the risk of progression to advanced fibrosis (assessed by noninvasive simple serum markers) (OR, 1.36; $p < 0.001$), whereas the use of oral diabetes agents, angiotensin 2 receptor blockers, and fibrates was associated with reduced risk (ORs, 0.92, 0.94, and 0.90, respectively; all $p < 0.05$).[12] Interestingly and importantly, ACEIs have also reduced morbidity and mortality in patients with cancer. A study of 153 patients with HCC who received radiofrequency ablation found that patients' overall survival was significantly better if they received ARBs and was numerically better if they received ACEIs; median time to recurrence of HCC was also significantly better in those who had received ARBs.[13] In a small, prospective, randomized, open-label trial, patients with HCC were randomized either

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; RAAS, renin-angiotensin aldosterone system; sHR, subdistribution HR.

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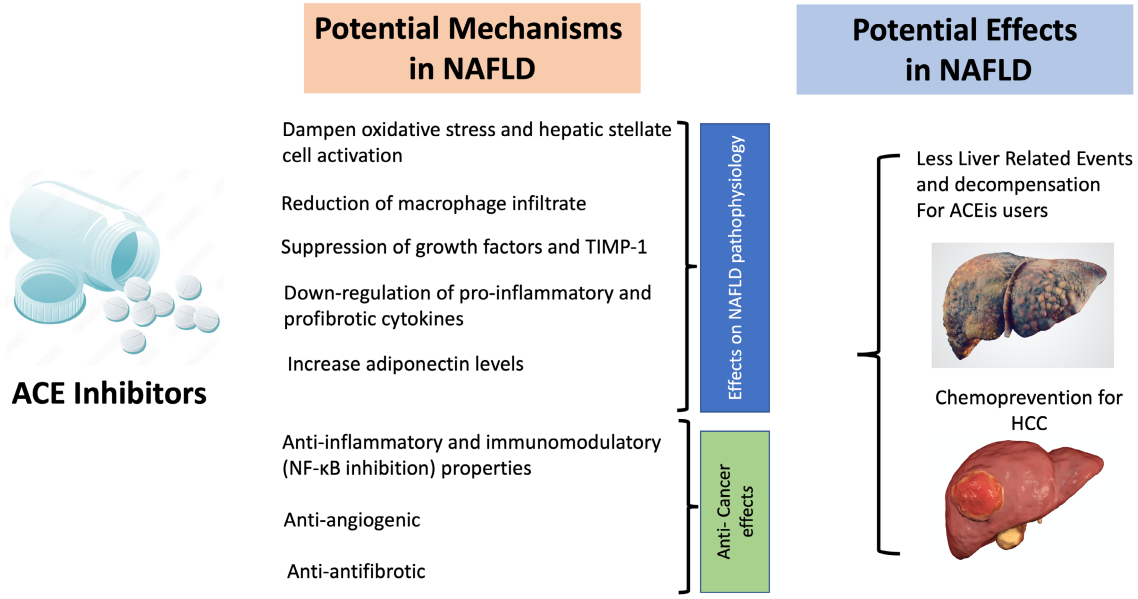

FIGURE 1 Mechanisms and effects of angiotensin-converting enzyme (ACE) inhibitors in NAFLD

to ACEIs plus vitamin K or no treatment; the cumulative HCC recurrence rate was lower in the ACEI-treated patients than in untreated patients (~40% vs. 75% recurrence [$p < 0.01$]).[14]

The study by Zhang et al.[3] is one of the largest retrospective observation studies to evaluate the effects of ACEIs and ARBs in patients with NAFLD. The beneficial effect of ACEIs on liver-related events, HCC, and cirrhosis complications, coupled with the established role of both circulating and local RAAS on the pathogenesis of NAFLD and NASH, has created considerable interest in the therapeutic potential of ACEI for NASH, particularly because ACEIs are widely used to treat medical comorbidities of NASH, are reasonably inexpensive, and have an excellent safety profile. ACEIs are already a cornerstone in the prevention and treatment of cardiovascular disease, hypertension, and complication of diabetes mellitus and certain chronic kidney disease. Improving the medical co-morbidities of NAFLD, either directly or indirectly, and potentially through treatment of shared pathogenic drivers of end-organ injury of metabolic syndrome, can improve the outcomes of patients with NAFLD/NASH. The previously unrecognized benefit of ACE on NAFLD raises some compelling questions regarding ACEI use contributing to variances in the natural history of disease, unpredicted placebo effectiveness in large, randomized trials, and future trial design for emerging therapies for NAFLD/NASH. Furthermore, the potential for synergistic effect of ACEI with other drugs to optimize the metabolic syndrome, improve insulin sensitivity (i.e., glucagon-like peptide 1, metformin, sodium-glucose transport protein 2), decrease lipids (i.e., statins), and/or their potential role in combination therapy with emerging antisteatotic, anti-inflammatory, and/or antifibrotic therapies for NASH requires further investigation.

Zhang et al.[3] used excellent methodological approaches to address biases by applying propensity scores and using absolute standardization difference to assure balances in the propensity scores. Nevertheless, we should be reminded of the weaknesses associated with observational studies that use International Classification of Diseases (ICD) codes, especially in the NAFLD field. First, the prevalence of NAFLD diagnosis based on ICD coding risks underreporting of the true prevalence of the disease in the population of interest. Second, despite the development of liver-related outcomes in the study cohort leading to liver-related mortality, no liver transplantations were performed in this cohort; this discrepancy may be due to various social, cultural, religious, and economic factors, which account for the low rate of deceased donation and acceptance of liver transplantation. Third, the incidence of HCC (2.1%) is higher than the incidence of cirrhotic complications (1.9%) and quite different from the natural history data of a large cohort of patients in the NASH Clinical Research Network.[1]

Despite these biases and variances in study cohort and outcomes, the study by Zhang et al. lends justification for using the drug as a potential chemoprevention agent for HCC and to decrease risk of hepatic decompensation. While it remains too premature to recommend ACEI as a primary prophylaxis in NAFLD/NASH, the provocative study by Zhang et al.[3] lends justification for further basic and clinical/translational studies to better define the pathogenic mechanism underlying the effects of ACEIs, and, more importantly, the conduct of randomized controlled trials on the effects of ACEIs on

liver-related events, cirrhosis, and HCC. In parallel, further questions regarding study designs in NAFLD, need for stratification by ACEI use, and potential for synergistic effects when ACEIs are combined with other antimetabolic therapies in a "cocktail" of treatment(s) for complications of metabolic syndrome warranted further investigation. Further questions regarding which ACEIs, as well as target dose and duration of therapy, have the most protective effect against NAFLD-related fibrosis and HCC warrants further investigation.

Often, good research raises more questions than it answers. While Zhang et al. are to be commended on broadening our understanding of the potential role of ACEIs and ARBs in NAFLD, much more lies ahead as we strive to unravel the complexities of NAFLD/NASH and identify safe, cost-effective therapies that are suitable for long-term use for the large population of patients with NAFLD/NASH.

CONFLICT OF INTEREST

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Mazen Noureddin[1]
Manal F. Abdelmalek[2]

[1]*Fatty Liver Program, Karsh Division of Gastroenterology and Hepatology, Comprehensive Transplant Center, Cedars Sinai Medical Center, Los Angeles, California, USA*
[2]*NAFLD Clinical Research Program, Division of Gastroenterology & Hepatology, Duke University, Durham, North Carolina, USA*

Correspondence
Mazen Noureddin, Fatty Liver Program, Karsh Division of Gastroenterology and Hepatology, Comprehensive Transplant Center, Cedars Sinai Medical Center, 8900 Beverly Blvd., Los Angeles, CA 90048, USA.
Email: Mazen.Noureddin@cshs.org

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