Letter to Editor

"Allopurinol and Liver Cirrhosis Complications: A Call for Further Investigation"

To the Editor,

Cirrhosis signifies the final stage of liver disease, defined by unalterable widespread liver fibrosis and the development of regenerative nodules. As it advances, complications such as jaundice, ascites, encephalopathy, and variceal bleeding become apparent, signifying a more advanced stage and a worse prognosis.[1] The phrase 'decompensated liver disease' is frequently used to describe the occurrence of any of these symptoms, which together indicate a substantial deterioration in liver function, often requiring immediate medical attention.

The recognized relationship between gut microbiota and liver metabolism, known as the gut-liver axis, is disturbed in cirrhosis. This results in a notable imbalance in the intestinal microbiota, a condition referred to as dysbiosis. This pathological condition involves significant changes in both the composition and functionality of the intestinal microbiota, which worsens the complications linked with cirrhosis.[2]

Patients with cirrhosis exhibit elevated oxidative stress in their intestinal mucosa, which can be traced back to heightened xanthine oxidase (XOR) activity. This increase in XOR activity, especially prominent during active liver disease phases, closely aligns with liver transaminase levels, particularly serum ALT. These findings suggest an intensified state of oxidative stress and inflammation. Furthermore, the elevated plasma XOR activity likely mirrors damage to hepatocytes and bile duct epithelial cells, thereby exacerbating liver injury.[3] Moreover, the induction of hepatic fibrosis by reactive oxygen species (ROS) occurs through the activation of hepatic stellate cells, leading to an exaggerated production of extracellular matrix proteins, consequently contributing to the progression of fibrosis, cirrhosis, and ultimately hepatocellular carcinoma.[4] Hence allopurinol, a xanthine oxidase inhibitor, could potentially be a life-changing protocol in cirrhosis patients.

In a recent 2023 study, one hundred patients with hepatic decompensation were randomly assigned in a 1:1 ratio to receive either allopurinol 300 mg or placebo tablets once daily for 6 months. The results demonstrated that after six months of treatment, allopurinol significantly reduced the risk of experiencing any first complication by 56% (hazard ratio [HR] 0.44; 95% confidence interval [CI], 0.27-0.62; $p < 0.001$). Moreover, allopurinol notably decreased the risk of overt ascites by 67% (HR 0.33; 95% CI, 0.0098-0.94; $p = 0.039$), spontaneous bacterial peritonitis by approximately 75% (HR 0.25; 95% CI, 0.05-0.76; $p = 0.01$), and hepatorenal syndrome by 80% (HR 0.2; 95% CI, 0.04-0.87; $p = 0.033$).[5]

Cirrhosis stands among the top ten causes of death in Africa, Southeast Asia, Europe, and the Eastern Mediterranean. Globally, it ranks as the 15th leading cause of disability-adjusted life-years (DALYs). Additionally, cirrhosis represents a significant financial burden, with liver-related costs in the US reaching $32.5 billion in 2016, the majority of which were allocated to inpatient or emergency care.[6]

Liver transplantation, although regarded as the optimal treatment for liver cirrhosis, remains challenging to access due to its high cost and prolonged waiting periods. Currently, less than 10% of the global demand for organ transplantation is met,[7] especially in developing nations where patients often succumb while awaiting a compatible donor. Allopurinol, a cost-effective remedy, presents a promising opportunity to extend the time before complications arise and enhance the overall quality of life for cirrhosis patients. Despite ongoing research efforts, progress has been slower than anticipated, necessitating further clinical trials involving larger cohorts and more comprehensive investigations. Additionally, exploring potential synergies between allopurinol and existing cirrhosis therapies could offer significant benefits. Further research endeavors could also delve into identifying specific patient subgroups, such as those with distinct etiologies or comorbidities, to learn whether they stand to gain greater advantages from allopurinol treatment, thus guiding targeted therapeutic approaches.

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