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EDITORIAL

Alcoholic hepatitis: should we combine old drugs for better results?

Joaquin Cabezas[1] · Ramon Bataller[1]

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Alcoholic liver disease (ALD) is the main cause of cirrhosis worldwide [1]. Despite its high prevalence, ALD has received little attention in the liver community and there is a clear lack of programs for early detection and novel targeted therapies for advanced forms. ALD encloses a wide spectrum of features, ranging from simple steatosis, steatohepatitis, and cirrhosis to hepatocellular carcinoma [2]. Patients with underlying ALD and heavy alcohol intake can develop an episode of alcoholic hepatitis (AH), the most severe form of ALD [3]. AH is characterized by an abrupt onset of jaundice and/or liver decompensation. Patients with AH often show signs of systemic inflammation at admission, and are prone to infections and kidney injury, which can lead to multi-organ dysfunction within a few days [4]. In its severe form, AH can result in 20–50 % mortality at 3 months. The only available therapies that improve survival are corticosteroids and liver transplantation [5, 6]. The efficacy of pentoxifylline is debatable, based on recent large clinical trials [6]. The efficacy of prednisolone has been shown in meta-analyses of individual data and was partially confirmed in the recent STOPAH trial [6, 7]. Unfortunately, many patients do not respond to prednisolone and performing salvage liver transplantation is not feasible in most centers. Therefore, there is an urgent need to provide these patients with novel targeted therapies. In the last two decades, there have been several attempts to test old and novel drugs in patients with severe AH, ranging from classic drugs [8] to monoclonal antibodies [9] or stimulating factors [10] to bone marrow transplantation [11]. While some of them have improved short-term mortality, the results have not yet been confirmed in independent cohorts. Since prednisolone consistently improves the 1-month survival in patients with severe AH, a common strategy is to add other drugs that could target some pathogenic driver in this disease such as anti-TNF drugs like Infliximab, which have been tested in combination with prednisolone [9]. While the initial results were encouraging, the usage of a high dose of TNF blocking agents increased the patient's mortality, likely through the increase of severe bacterial infections [12].

One of the hallmark consequences of alcohol abuse is the induction of marked oxidative stress in the liver. Alcohol is known to stimulate reactive oxygen species (ROS) by activating NADPH oxidase and CYP2E1 among other oxidant pathways [13, 14]. Moreover, advanced liver disease is characterized by defective antioxidant systems including hepatocellular content in glutathione (GSH). GSH is an important antioxidant in plants, animals, fungi, and some bacteria. GSH reduces disulfide bonds formed within cytoplasmic proteins to cysteines by serving as an electron donor. Once oxidized, GSH can be reduced back by glutathione reductase, using NADPH as an electron donor. The ratio of reduced glutathione to oxidized glutathione within cells is often used as a measure of cellular oxidative stress [15]. Of note, there are important determinants of AH other than oxidative stress, including immune cell activation and inflammatory mediators release, intestinal microbiome changes and leaky gut-bacterial translocation, attraction of neutrophils, and release of danger signals [i.e. pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs)] [16]. Therefore, it is conceivable that effective drug therapies for AH should target multiple pathophysiological pathways other than oxidative stress.

✉ Ramon Bataller
bataller@med.unc.edu

[1] Departments of Medicine and Nutrition, Liver Center, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA

Based on experimental studies indicating that severe ALD is associated with decreased GSH synthesis and resulting oxidative stress [17], Nguyen-Khac et al. performed a large clinical trial using *N*-acetyl cysteine (NAC) (a drug that provides cysteine for glutathione synthesis) in combination with prednisolone [18]. In this important study, NAC administration reduced the development of infections and hepatorenal syndrome and decreased 2-month mortality. This study strongly suggests that replenishing GSH could be beneficial in patients with severe AH receiving prednisolone. Whether the use of antioxidants alone is able to improve survival in patients with AH is controversial [19, 20]. While the study by Phillips et al. [19] showed no beneficial effect, a clinical trial by Stewart et al. [20] showed improved short-term outcome. Further studies including end-points other than survival are clearly needed to assess the efficacy of antioxidants in alcoholic liver disease including AH.

An alternative approach to treat conditions associated with depleted GSH is the use of S-adenosylmethionine (SAMe). SAMe, which is well tolerated as an oral presentation, is a co-substrate involved in methyl group transfer and has been shown to increase cellular GSH content in diseases characterized by GSH depletion, such as alcoholic liver disease [21]. SAMe is a precursor for the synthesis of cysteine and thus is required for the generation of GSH [22]. In this issue of *Hepatology International*, Tkachenko et al. [23] performed a clinical trial adding SAMe, a drug with similar biological effects compared with NAC, to prednisolone. In the current study, 40 patients with severe AH were randomized to receive prednisolone alone or in combination with SAMe for 1 month, continuing the latter for another month. The primary end-point of the study was 1-month mortality. The initial response, as assessed by the Lille model, was much better in patients receiving SAMe (95 vs. 65 %). Although there was a trend to reduce 1-month mortality (0 vs. 10 %), the primary end-point was not reached given the low number of patients. Interestingly, hepatorenal syndrome occurred in 20 % of the prednisolone group, while no cases were registered in the combination group. The results of this interesting study suggest that refilling GSH increases the efficacy of prednisolone in patients with AH.

The results of the current study reveal a crucial role for antioxidant defenses in the pathogenesis of AH. Alcohol abuse is associated with an increased production of ROS and efficient and intact antioxidant systems are essential to protect hepatocytes from cell death [24]. Depletion of GSH, a key antioxidant molecule, could favor the accumulation of ROS and the resulting oxidative stress. It is well known that oxidative stress plays a role in the main pathogenic events in AH. First, it favors hepatocellular death in animals exposed chronically to ethanol, a key feature of AH. Second, it stimulates hepatic stellate cells to produce excessive amounts of collagen and induces the diffusion of hepatic fibrosis [25]. And, finally, it is associated with an increased rate of bacterial infections [26]. An additional potential benefit of antioxidants in the setting of cirrhosis and AH is the prevention of hepatorenal syndrome. The fact that systemic inflammation precedes and predicts the development of renal failure in patients with AH supports this hypothesis [4]. Finally, antioxidants such as SAMe could be beneficial in patients with alcoholic cirrhosis regardless of the presence of superimposed AH. In these lines, Mato et al. [27] tested the utility of long-term administration of SAMe in patients with alcoholic cirrhosis. This study showed that prolonged treatment SAMe may improve survival in patients with less advanced alcoholic liver cirrhosis, such as Child A and B patients.

Although the study by Tkachenko et al. yielded promising results, clinical trials with well-characterized patients with AH that include a larger number of patients are needed to conclude that SAMe should be indicated in this setting. Moreover, it is possible that longer follow-up periods (up to 3 months) are needed to reach higher mortality rates. Future studies should also measure the degree of oxidative stress in the liver and systemically to identify those patients that would benefit from antioxidant therapies. In this regard, the combination between Silymarin and SAMe has been recently brought to market, and this combination appears to have a promising effect on patients with ALD [28]. Prospective clinical trials in patients with ALD are needed to test this therapeutic approach.

In conclusion, the study by Tkachenko et al. showed that the addition of SAMe to prednisolone improves the short-term outcome of patients with AH. This study, in conjunction with the previous one showing the beneficial effects of NAC, indicates that targeting oxidative stress might be beneficial to patients with this devastating clinical condition. Based on the available data, the use of antioxidants to treat AH cannot as yet be strongly recommended. Whether the use of antioxidants (NAC and SAMe) in combination with prednisolone improves survival requires larger clinical trials.

Conflicts of interest Joaquin Cabezas and Ramon Bataller disclose no conflicts.

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