Editorial

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Restoration of bactericidal activity of neutrophils by myeloperoxidase release: A new perspective for preventing infection in alcoholic cirrhosis

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Advances in the management of decompensated cirrhosis have dramatically improved patient outcomes in the past years. Significant progress has been made in the management of gastrointestinal bleeding, severe alcoholic hepatitis, hepatorenal syndrome and the management of patients in the intensive care unit. Nevertheless, decompensated cirrhosis is still associated with a high risk of short-term death. Severe infection is one of the major causes of mortality. For example, patients with cirrhosis were shown to have a higher probability of dying from sepsis (relative risk of 2) compared to those without cirrhosis in a large series from the USA [1]. In the specific setting of severe alcoholic hepatitis treated with corticosteroids, patients who develop infection after the initiation of treatment have a lower survival at 2 months than those who do not (relative risk of death of around 1.5) [2]. It is interesting to note that patients who do not respond to corticosteroids have a far higher risk of developing infection than responders (relative risk of 4). This suggests that patients with the greatest impairment in liver function have a higher probability of developing infection during follow-up. The relationship between severely impaired liver function and the risk of infection has been confirmed in a pooled analysis of studies performed in decompensated cirrhosis [3]. Thus, any improvement in liver function should result in a lower incidence of infection. However, in patients with alcoholic cirrhosis, the only strategy that has been shown to be associated with an improved prognosis is withdrawal from alcohol, even in patients with very severe liver impairment [4]. Nevertheless, many of these patients do not improve and die or require liver transplantation after a short period of time.

A new concept in the management of patients with cirrhosis, whatever the origin of underlying disease, is so-called acute-on-chronic liver failure (ACLF). This acute decompensation of cirrhosis is associated with a mortality that can reach 90% at one month in the most severe form, which is classified as ACLF-3 [5]. In this subgroup of patients, alcoholic cirrhosis is the leading cause of underlying liver disease and the precipitating event of ACLF is infection in about 50% of cases. Considering that ACLF in general and sepsis in particular are associated with multiorgan failure (encephalopathy, kidney injury, circulatory failure etc.) and immune paralysis [6], any strategy to prevent this severe deterioration would be of great interest for the management of these patients.

The prognosis of sepsis has improved along with the global management of cirrhosis due to several factors such as a better and earlier diagnosis, new antibiotics and the prevention of hepatorenal syndrome [7]. Thus, mortality has decreased by 10% in the past few years but remains high. It is important to mention that the management of sepsis in cirrhosis is essentially focused on treatment rather than prevention. Indeed, the prevention of infection in cirrhosis is restricted to antibioprophylaxis for gastrointestinal bleeding and after a first episode of spontaneous peritonitis. Most of the few ongoing studies to evaluate the prevention of infection in cirrhosis are testing probiotics or new antibiotic regimens (www.clinicaltrials.gov). So far, there is no strategy to restore the immune defects associated with cirrhosis. This immune dysfunction is multifactorial and extremely complex because it associates systemic inflammation, characterized by neutrophil burst, elevated circulating cytokines and activated blood white cells, which is counterbalanced by a relative immune deficiency (e.g. damage of circulating immune cells and a defect in hepatic synthesis of immunity proteins) [8]. To date, no strategy has been shown to trigger this immune defect.

This issue of the *Journal of Hepatology* includes a study with the goal to dissect the pathways associated with a functional defect of polymorphonuclear neutrophils in alcoholic cirrhosis. This translational study is based on human samples from patients with decompensated alcoholic cirrhosis (Child-Pugh class B and C). Boussif *et al.* provide evidence for altered release of myeloperoxidase in patients with alcoholic cirrhosis compared to healthy controls. However, one could suggest that the choice of controls is not fully appropriate. Indeed, this raises the question of the selectivity of the functional defect of neutrophils: is it related

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to cirrhosis by itself, to liver decompensation or to the alcoholic etiology? Although an ideal study would test neutrophils from populations with different severities and etiologies of cirrhosis, by definition, studies are dependent upon recruitment from the medical unit where the blood samples are collected and many translational studies have not overcome this limitation.

In terms of mechanisms of action, Boussif *et al.* show that patients with decompensated cirrhosis do not have a defect in myeloperoxidase production, but present instead with a defect in cellular signaling leading to lower myeloperoxidase exocytosis. This defect is associated with a reduced capacity to kill bacteria in neutrophils from patients with cirrhosis, which is demonstrated by the incubation of neutrophils with *E. coli*. This paper nicely shows that this defect in myeloperoxidase release and bacterial killing is reversible following administration of CL097, a TLR7/8 agonist. Using this stimulation, neutrophils from patients with alcoholic cirrhosis have the same properties as healthy controls. This study contributes to our knowledge of the immune defense against infection in decompensated alcoholic liver disease and, in association with the data on blockade of PD-1 and TIM-3 in alcoholic hepatitis reported by Markwick *et al.* [9], this study suggests that immunodeficiency is reversible.

It is important to keep in mind that neutrophils have different functions in alcoholic liver disease. Besides their crucial role in the host defense against pathogens, these cells are central in the pathogenesis of alcoholic hepatitis. Alcohol-induced liver injury is characterized by neutrophil recruitment driven by the activation of Kupffer cells via bacterial translocation (mostly lipopolysaccharide LPS), and also hepatocyte damage, oxidative stress and lipid peroxidation [10]. Neutrophil infiltrates are one of the key hallmarks of the histological diagnosis of alcoholic hepatitis with Mallory-Denk bodies and hepatocyte ballooning [11]. Besides this apparent paradox, future studies are strongly needed to investigate why the same cell can be regarded as beneficial against infection and detrimental in terms of exacerbated liver inflammation in the same patient.

The study by Boussif *et al.* provides new therapeutic perspectives in alcoholic cirrhosis because restoration of the antibacterial properties of the immune system by the TLR7/8 agonist. This can be considered a potential new target for patients with severe liver dysfunction. Thus, future management of decompensated cirrhosis could be viewed as a combination of several targets: improving liver function, restoring immune paralysis, targeting liver inflammation, promoting liver regeneration and treating complications. This is an exciting prospect because recent medical progress has mainly involved the treatment of complications.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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