EDITORIAL

More Than Meets the Eye in Using Interleukin 6 as a Marker of Inflammation and Prognostic Factor for Patients With Cirrhosis

Inflammation is considered the driving force of many acute and chronic conditions, including among others sepsis, atherosclerosis, chronic kidney disease, chronic pulmonary diseases, and cancer.[1] In the liver, inflammation plays a key role in most causes of acute liver injury and in the progression of acute to chronic injury and subsequent development of liver fibrosis.[2] Recent studies in human cirrhosis indicate that, besides inflammation within the liver tissue, there is an enhanced systemic inflammation that contributes to cirrhosis progression and death. Thabut et al[3] first showed that in patients with functional renal failure (most of them having hepatorenal syndrome) the existence of systemic inflammation, as assessed by systemic inflammatory response syndrome (SIRS), was associated with poor outcome, independently of the existence of sepsis. These observations were later extended to alcoholic hepatitis by showing that patients with SIRS at admission to hospital not only had poor prognosis compared with those without SIRS, but also an increased risk of developing acute kidney injury during hospitalization, thus demonstrating a link between inflammation and organ dysfunction outside the liver.[4,5] The existence of a relationship between SIRS and other complications of cirrhosis, particularly hepatic encephalopathy, has also been demonstrated.[6] Moreover, systemic inflammation, assessed by SIRS, plasma C-reactive protein, or urinary monocyte-chemoattractant protein-1, is associated with increased mortality and hospital readmission.[7–9] It is important to remark that in cirrhosis, SIRS is not always synonym with infection. Thus there are patients with cirrhosis and infection who do not have SIRS; and patients with SIRS who do not have infection. Although not completely understood, evidence indicates that SIRS in cirrhosis is caused by translocation of bacteria or bacterial products from the gut to bacterial lymph nodes and systemic circulation that would then stimulate the immune system through the activation of pattern-recognition receptors expressed in immune cells.[10]

Systemic inflammation also seems to play an important role in sudden deterioration in patients with cirrhosis leading to development of acute-on-chronic liver failure (ACLF), a common syndrome characterized by hepatic and/or extrahepatic organ failure and high short-term mortality.[11] Studies with large cohorts of patients have shown that systemic inflammatory response occurs in cirrhosis, particularly in the setting of ACLF, and is associated with multiorgan dysfunction and increased risk of death (reviewed in [11]). Moreover, the plasma levels of several inflammatory and anti-inflammatory cytokines and chemokines are significantly increased in patients with ACLF compared with patients with decompensated cirrhosis without ACLF and some of them correlate with survival.[12,13] Cytokines and chemokines preferentially increased in ACLF are tumor necrosis factor-α, interleukin (IL) 6, IL8, MCP-1, interferon gamma-induced protein-10, macrophage inflammatory protein-1β, granulocyte colony–stimulating factor, granulocyte-macrophage colony–stimulating factor, IL10, vascular cell adhesion molecule-1, vascular endothelial growth factor-A, eotaxin, IL2, and fraktalkine. Most of these substances are related to innate immune response processes, such as leukocyte migration, particularly monocytes and macrophages, and chemotaxis pathways, whereas others are markers of endothelial dysfunction.[12,13] In a large cohort of patients with and without ACLF included in the Canonic study, IL6 levels correlated strongly with some important clinical outcomes, such as renal failure, SIRS, and bacterial infection. Moreover, logistic regression analysis of all cytokines evaluated showed that only IL6 and IL8 had independent association with ACLF severity and mortality.[13] Similar data have been reported in a recent study on neutrophil dysfunction in ACLF patients, where inflammatory cytokines/chemokines, including IL6, IL17, IL23, and 20 chemokine (C-Cmotif) ligand 20-20, were significantly increased. In fact, IL23 levels were found to closely correlate with IL6 levels, Child Turcotte Pugh scores, and mortality. Blockage of the CXC chemokine receptor 1/2 abrogated the liver damage in ACLF.[14]

In this context, the study of Remmler et al[15] published in this issue of *Clinical Gastroenterology and Hepatology* assessing the value of IL6 levels in predicting mortality in cirrhosis is of clinical and mechanistic relevance. IL6 is a pleiotropic cytokine that may exert multiple functions in the body.[16] In the liver, main functions of IL6 include liver regeneration, infection defense, and metabolic homeostasis. IL6 is synthetized during inflammatory conditions mainly by monocytes and macrophages on stimulation of toll-like receptor-4 by lipopolysaccharide or by IL1 or tumor necrosis factor-α. In the setting of an acute inflammation, IL6 is the major inducer of acute phase proteins in the liver.[16] Evidence also suggests that persistent activation of the IL6 pathway may have detrimental effects in the liver and in other tissues.[16] In cirrhosis, increased serum levels of IL6 were first reported by Devière et al[17] in 1989. Since then, several studies have shown that IL6 plasma levels are increased in patients with advanced cirrhosis, particularly in those with bacterial infections.[18–20] Moreover, high plasma IL6 levels have been shown to correlate with important outcomes,

specifically, kidney failure, ACLF, and mortality, as described previously. Regrettably, information from these relevant publications was not discussed in the study by Remmler et al.[15] The main strengths of the report of Remmler et al[15] are the assessment of the prognostic value of IL6 in a large cohort of patients with cirrhosis being evaluated for liver transplantation and the comparison of the predictive value of IL6 with that of the most common tools used in prognosis assessment in cirrhosis, particularly Model for End-Stage Liver Disease (MELD) and MELDNa scores. The results of the study show that IL6 levels are associated with mortality and that their prognostic value was better than that of C-reactive protein levels and leukocyte count. Interestingly, IL6 levels had an excellent negative predictive value of mortality. Although this is important information, it is intriguing that IL6, one of the many markers of inflammation, singularly is superior to indices of organ failures and homeostatic derangements, such as MELD and MELDNa for predicting 360-day mortality. A careful look at the data shows a very wide confidence interval in the reported IL6 values in the 3 categories studied (Q2, Q3, and Q4). It is difficult to comprehend how a test could be considered so reliable with such a large variability. Moreover, there was considerable overlap between IL6 levels in the 3 groups. However, the ranges were much smaller with C-reactive protein and white blood cell levels. White blood cell levels surprisingly did not show any reflection of inflammation in the cohort of patients studied. The findings of Remmler et al[15] obtained from a retrospectively studied cohort therefore need to be taken with a pinch of salt and must be validated in prospective series with well-defined populations.

Another important concern about the role of IL6 as a predictor of mortality in cirrhosis is the multidimensional potential of IL6. The IL6 is one of the most potent initiators of hepatic regeneration. High IL6 levels do not necessarily relate to inflammation alone. Whether the hepatic parenchyma in cirrhosis is inflamed or is attempting to regenerate remains unknown based on the data from the study by Remmler et al.[15] Furthermore, the authors have not provided information on tumor necrosis factor-α levels, which closely parallels IL6 dynamics. In fact, both these cytokines are known to be released by stimulation of the Kupffer cells and other immune cells by lipopolysaccharide.

Several other important questions remain open. (1) Is IL6 just a marker of poor outcome or is it detrimental in itself to hepatic and nonhepatic organ function and therefore persistent activation of IL6 participates in cirrhosis progression? (2) Could IL6 levels be used as biomarker of disease progression? In this regard, findings from the Canonic study showed that IL6 levels decrease in patients after recovery from ACLF, whereas they increase in patients with worsening ACLF.[13] (3) Could IL6 be a potential biomarker to monitor the effects of new therapies to prevent cirrhosis progression? (4) Is IL6 a biomarker of inflammation in cirrhosis, in patients with and without infections? (5) Should IL6 pathway be considered a target for therapeutic intervention in cirrhosis? Although the study by Remmler et al[15] has drawn attention to the role of ongoing inflammation in progression of cirrhosis, several concerns as stated need to be addressed before IL6 can be accepted as a reliable biomarker of systemic inflammation in cirrhosis.

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Conflicts of interest

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