Commentary

Extracorporeal liver support: a continuing challenge

Ram M Subramanian[1] and John A Kellum[2]

[1]Departments of Pulmonary & Critical Care and Gastroenterology & Hepatology, University of Chicago, 5841 South Maryland Ave., MC 6076, Chicago, IL, 60637, USA
[2]Department of Critical Care Medicine, 608 Scaife Hall, University of Pittsburgh School of Medicine, 3550 Terrace Street, Pittsburgh, PA 15261, USA

Corresponding author: John A Kellum, kellumja@ccm.upmc.edu

Published: 29 January 2007
This article is online at http://ccforum.com/content/11/1/106

Critical Care 2007, **11:**106 (doi:10.1186/cc5143)

See related research by Stadlbauer *et al*., http://ccforum.com/content/10/6/R169

Abstract

Given that liver failure continues to pose an enormous clinical challenge, the concept of hepatic dialysis has enjoyed significant interest. In particular, many investigations have examined the therapeutic mechanisms and efficacy of artificial albumin dialysis based systems in acute on chronic liver failure, the results of which have been conflicting. Albumin dialysis systems do not appear to significantly decrease serum concentrations of inflammatory cytokines in severe acute on chronic liver failure. Thus, if these treatments do result in clinical improvement, then other therapeutic mechanisms must be involved.

In a previous issue of *Critical Care*, Stadlbauer and colleagues [1] examined the effects of two artificial albumin dialysis systems on the removal of cytokines in the setting of acute on chronic liver failure. In the absence of liver transplantation, patients with liver failure face limited therapeutic interventions and ultimately suffer multiple organ system dysfunction. The shortage of donor livers and the growing number of patients with advanced liver disease has stimulated active interest in extracorporeal liver support devices, including artificial and bio-artificial systems. Although artificial support systems have focused primarily on albumin dialysis techniques to achieve detoxification, bio-artificial systems potentially have the added advantage of simulating the liver's synthetic functions. Although no large multicentered trials have yet established the role of liver assist devices, a large systematic review [2] suggests that artificial liver support systems reduce mortality in acute on chronic liver failure compared with standard medical therapy. This finding has led investigators to focus their attention on the potential mechanisms of therapeutic benefits of artificial assist devices in acute on chronic liver failure, including removal of proinflammatory cytokines [3].

This area of investigation has been addressed in other small studies, with conflicting results. For example, one recent study [4] suggested a decrease in serum cytokine levels following treatment, with an associated improvement in patient prognosis, whereas a second recent study [5] found no effect of treatment on cytokines. A crucial factor influencing the outcome of these studies is the severity of liver disease, as measured objectively using the Mayo End Stage Liver Disease score, which may correlate with the 'cytokine burden'. In the study by Stadlbauer and colleagues included in a previous issue [1], the patient population is characterized by a high degree of disease severity, as evidenced by a mean Mayo End Stage Liver Disease score of 31. Unfortunately, the study demonstrates no efficacy of artificial liver support systems in decreasing cytokine levels, and the authors conclude that a high rate of cytokine production that exceeds the rate of detoxification probably accounts for their findings.

Indeed, the results of the study by Stadlbauer and colleagues [1] are reminiscent of early studies of hemofiltration for treatment of sepsis [6], several of which revealed that cytokine clearance was possible but removal rates were insufficient to permit meaningful changes in plasma concentrations [7]. Results from clinical studies similarly did not support a role for low volume, 'renal dose' hemofiltration for treatment of sepsis [8]. The reasons for the relatively poor clearance of interleukin-6 with the MARS™ (Gambro AB, Stockholm, Sweden) and Prometheus™ (Fresenius Medical Care AG & Co. KGaA, Homburg, Germany) systems are uncertain. Much greater clearance has been reported with large-pore hemofiltration in animals and with associated physiologic improvement [9]. However, clearances for interleukin-10 (Prometheus™) and tumor necrosis factor (TNF; both systems) were significantly better. The reason why these clearances did not translate into changes in plasma concentrations was probably not related to high production

TNF = tumor necrosis factor.

rates, as suggested by the authors, because circulating levels were low (TNF levels were near normal) and endogenous clearance was almost certainly impaired. Instead, the lack of efficacy could be related to the short treatment time, the removal of circulating inhibitors (such as soluble TNF receptors), or even enhanced production of mediators in response to treatment.

Nevertheless, despite its small sample size, the study by Stadlbauer and colleagues [1] suggests that if liver assist therapy is effective, then mechanisms other than cytokine removal must be important. The field of bio-artificial liver support has been an area of active investigation [10], and the prospect of an extracorporeal device that will reproduce both the synthetic and detoxification functions of the liver will sustain continued research in this field.

Competing interests

The authors declare that they have no competing interests.

References

1. Stadlbauer V, Krisper P, Aigner R, Haditsch B, Jung A, Lackner C, Stauber RE: **Effect of extracorporeal liver support by MARS and Prometheus on serum cytokines in acute-on-chronic liver failure.** *Crit Care* 2006, **10:**R169.
2. Kjaergard LL, Liu J, Als-Nielsen B, Gluud C: **Artificial and bioartificial support systems for acute and acute-on-chronic liver failure.** *JAMA* 2003, **289:**217-222.
3. Sen S, Davies NA, Mookerjee RP, Cheshire LM, Hodges SJ, Williams R, Jalan R: **Pathophysiological effects of albumin dialysis in acute-on-chronic liver failure: a randomized controlled study.** *Liver Transpl* 2004, **10:**1109-1119.
4. Di Campli C, Zocco MA, Gaspari R, Novi M, Candelli M, Santoliquido A, Flore R, Tondi P, Proietti R, Gasbarrini G, *et al.*: **The decrease in cytokine concentration during albumin dialysis correlates with the prognosis of patients with acute on chronic liver failure.** *Transplant Proc* 2005, **37:**2551-2553.
5. Ilonen I, Koivusalo AM, Hockerstedt K, Isoniemi H: **Albumin dialysis has no clear effect on cytokine levels in patients with life-threatening liver insufficiency.** *Transplant Proc* 2006, **38:** 3540-3543.
6. Kellum JA, Bellomo R: **Hemofiltration in sepsis: where do we go from here?** *Crit Care* 2000, **4:**69-71.
7. Kellum JA, Johnson JP, Kramer D, Palevsky P, Brady JJ, Pinsky MR: **Diffusive vs. convective therapy: effects on mediators of inflammation in patient with severe systemic inflammatory response syndrome.** *Crit Care Med* 1998, **26:**1995-2000.
8. Cole L, Bellomo R, Hart G, Journois D, Davenport P, Tipping P, Ronco C: **A phase II randomized, controlled trial of continuous hemofiltration in sepsis.** *Crit Care Med* 2002, **30:**100-106.
9. Lambermont B, Delanaye P, Dogne JM, Ghuysen A, Janssen N, Dubois B, Desaive T, Kolh P, D'Orio V, Krzesinski JM: **Large-pore membrane hemofiltration increases cytokine clearance and improves right ventricular-vascular coupling during endotoxic shock in pigs.** *Artif Organs* 2006, **30:**560-564.
10. Van de Kerkhove MP, Hoekstra R, Chamuleau RAFM, Van Gulik TM: **Clinical application of bioartificial liver support systems.** *Ann Surg* 2004, **240:**216-230.