



A new horizon for liver support in acute liver failure

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See Articles, pages 378–387 and pages 388–398

Acute liver failure (ALF) is a relatively uncommon disease usually affecting young people without preexisting liver disease. Its clinical spectrum includes not only severe derangement of liver function, but also multi-organ failure and a high risk of sepsis, explaining the strong association between ALF and mortality that exceeds 50% [1]. Liver transplantation is the only therapeutic approach that has shown a survival benefit in patients with severe ALF. However, the shortage of organs for transplantation or the existence of contraindications limits the applicability of the procedure. In addition, the need of long-life immunosuppressive therapy in these young patients associates a relevant long-term morbidity and mortality. On the other hand, when spontaneous resolution occurs, the liver usually recovers completely. Therefore it is not surprising that during the last decades, several attempts of providing temporary support of ALF patients have been described. In this context, the development of extracorporeal liver support devices would be important for maintaining the patient's condition until the spontaneous recovery of liver function occurs or until an organ becomes available. From a theoretical perspective, an effective extracorporeal liver support system should replace three major functions of the liver: detoxification, biosynthesis and regulation. In the setting of ALF, the main goals would be to remove putative toxins preventing further aggravation of liver failure, to stimulate liver regeneration and to improve the pathophysiological features of ALF [2]. Toxin removal by high volume plasmapheresis has been tested with some evidence of success, however it is difficult to draw conclusions on this approach as the single study performed in ALF has so far only been presented in abstract form [3].

Clinically, the goal should be to provide liver and support for other organs with the aim of avoiding transplantation or bridging the patient to the procedure in the best possible condition. Extracorporeal liver support systems clinically tested fall into two main categories: (i) the purely artificial systems that are based on the principles of adsorption and filtration and are aimed to remove circulating toxins by using a variety of membranes and adsorbents; and (ii) the bioartificial systems that are hybrid devices that incorporate liver cells/hepatocytes in order to

improve the detoxification capacity as well as to support the failing synthetic liver function [4].

Two large randomized trials specifically addressing the role of extracorporeal liver support in ALF have been published in the past years, one of them using a purely artificial device based in albumin dialysis (MARS) [5] and the other with a bioartificial device based on porcine liver cells (Hepat-assist) [6]. The endpoint of both trials was survival. Although mortality was lower in the experimental arm in both cases, the differences were non-significant. The Hepat-assist trial, including patients with fulminant and subfulminant liver failure as well as patients with primary non-function, was prematurely stopped due to futility although a post-hoc analysis showed a survival benefit in the subgroup of patients with fulminant or subfulminant liver failure. In the MARS trial, the high early transplantation rate could have had a confounding effect in determining the true level of efficacy.

Therefore, the potential role of extracorporeal liver support remains controversial. From a pathophysiologic point of view, it is possible to speculate that the efficacy of these devices in terms of providing an adequate liver support was insufficient, which suggests that more efficacious devices may have a greater impact in biology and in clinical outcomes of ALF patients. In this issue of the *Journal of Hepatology*, two studies have evaluated two different approaches in the treatment of an experimental model of ALF induced by the administration of D-Galactosamine (GALN) in large animals (mini-pigs) (Table 1).

It is interesting to note that both groups have elected to use the same mechanism of inducing ALF in their large animal model. The GALN model is well established and known to have a variety of effects beyond simply inducing hepatocyte damage. Although the GALN model may not be exactly representative of human ALF, it has the advantage (as demonstrated in both studies) of good reproducibility, which is important in keeping control of group sizes for both ethical and financial considerations. One feature of GALN toxicity is the substantial sensitization of the system to bacterial lipopolysaccharides (endotoxins) [7]. As such, the model can be considered to potentiate the effects of circulatory disturbances and dysfunction of secondary organs that may be observed subsequently to ALF.

The fact that both extracorporeal systems show significant improvements in survival over a relatively short period of time suggests that the primary beneficial effect in these models is detoxification. The capacity of a device for removal of toxins has always been a key consideration in the concept and design

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Editorial

Table 1. An outline of the two different approaches followed by Glorioso *et al.* & Zhou *et al.*

	Glorioso <i>et al.</i>	Zhou <i>et al.</i>
Animal model	D-galactosamine induced ALF in pigs	D-galactosamine induced ALF in pigs
Liver support approach	BAL support based on porcine hepatocyte spheroids	Low-volume plasma exchange with plasma filtration and adsorption
Study groups	Control Non-cell based artificial liver support BAL with porcine hepatocyte spheroids	Control Plasma filtration and adsorption Low-volume plasma exchange Low-volume plasma exchange with plasma filtration adsorption
Major outcome	Improve survival in BAL based system	Improve survival in low-volume plasma exchange with plasma filtration adsorption
Minor outcomes	Prevention of cerebral manifestations of ALF Less vasopressor requirements	Improvement in liver tests and attenuation of inflammatory response Improvement in liver regeneration
Major concerns	Risk of zoonosis	Filter efficiency

ALF, acute liver failure; BAL, bioartificial liver.

of previous systems. For those based on adsorbent columns, the question of saturation of the materials and hence the effective treatment times have been raised repeatedly [8]. Although the system reported by Zhou *et al.* utilizes a sorbent component to the system, its novel combination with plasma exchange appears to offer improved functionality and capacity to remove toxic metabolites. In the study by Glorioso *et al.*, it is the functional biomass rather than sorbent capacity that appears to be the key element for an effective therapy. This study uses primary cells rather than cultured cell lines which may also prove to be significant in the future development of bioartificial systems due to concerns over the amount of metabolic function retained by transformed cells [8]. Neither study indicates specifically which toxins are targeted and removed by their extracorporeal devices, but instead show a subsequent reduction in inflammatory markers such as cytokines and ammonia. Although there are many possible sources of inflammation that might be removed, considering that the GALN model is known to have enhanced sensitivity to bacterial endotoxins it may be reasonable to consider that these systems have some capacity to remove (or metabolise) these substances.

The duration of therapy also appears to be a determining factor for a positive outcome. In the spheroid hepatocyte system a single 24 hour treatment was found to be more effective with repeated 6 hour therapy sessions. This would suggest that the ability to provide continual support to an ALF patient rather than intermittent detoxification provides a more conducive environment for hepatic recovery/regeneration. The study of Zhou *et al.* did not examine variable treatment sessions, but the timing of duration of the therapy are likely to be integral to the success of the device. In both models the treatment was started after it could be shown that a threshold for ALF had been passed. It could be considered that in a clinical setting, the earlier that treatment could be initiated the more likely it is that pre-insult liver function could be restored.

It should be noted that both systems include the potential to supplement the subjects' albumin, either by introduction of exogenous plasma or by *de novo* synthesis by the hepatocytes. It has become evident in recent years that albumin performs a number of functions beyond that of plasma volume regulation, indicating that the design of future extracorporeal systems

should include the provision to renew or replace the patient's own protein [9]. Whether the design of new systems should include the provision to additionally supplement the patients' albumin to a nominal therapeutic level remains an open question. Though it should be considered that increasing the total metabolic transport capacity for the patient by increasing albumin levels should improve the rate at which harmful metabolites are carried to an extracorporeal device for detoxification.

Both groups indicate that they wish to progress to human studies, though as has been stated above [4], studies in ALF are complicated by subjects receiving a transplant before a conclusion on the effectiveness of a device can be determined. Whereas transplantation is a proven therapy, there is limited availability. Should an extracorporeal device be able to provide sufficient evidence of organ recovery, early in the timecourse of the ALF event, it may be possible to consider a study that examines non-transplant survival as an endpoint.

Should a device be able to effectively support ALF subjects to recovery then this would have substantial benefit in freeing organs for other recipients, as well as potentially providing cost savings for healthcare providers. If a device were to prove effective in the treatment of ALF, then its application across the spectrum of other severe liver diseases would naturally be the subject of great interest.

There are still a number of other systems in development, for both acute and acute-on-chronic applications, which suggests that there is a continuing interest both commercially and scientifically to fill this current unmet clinical need.

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