

Cytokines and liver failure: modification of TNF- and IL-6 in patients with acute on chronic liver decompensation treated with Molecular Adsorbent Recycling System (MARS)

Giovanni Ambrosino¹, Agostino Naso², Paolo Feltracco³, Paolo Carraro⁴, Stefano M. Basso¹, Sergio Varotto¹, Umberto Cillo¹, Giacomo Zanus¹, Patrizia Boccagni¹, Alberto Brolese¹, Mario Plebani¹, Giampiero Giron³, Davide F. D'Amico¹

¹ Department of Surgery and Gastroenterological Science, Liver Transplant Unit, University of Padova, Padova, Italy; ² Department of Nephrology University of Padova, Padova, Italy; ³ Department of Anesthesiology University of Padova, Padova, Italy; ⁴ Clinical Laboratory University of Padova, Padova, Italy

Abstract. Liver transplantation, considered today as the most effective treatment for end-stage liver diseases, can not always be performed on every patient affected with a liver disease. Patients with end-stage liver diseases, usually have high bilirubin, encephalopathy and renal failure. In these situations cytokines play an important role in different processes, from apoptosis to regeneration. The aim of this clinical study has been to analyse the action of new artificial liver system, called Molecular Adsorbent Recycling System (MARS) on cytokines metabolism in patients affected with acute on chronic liver failure. The results are intriguing because an increase of IL-6 and a decrease of TNF- α observed during MARS treatment. The study confirms the efficacy of MARS therapy in terms of homeostasis of the cytokines network and suggests an usefulness of monitoring their level during liver failure.

Key words: Liver failure, cytokines, Molecular Adsorbent Recycling System

Introduction

Severe hepatic failure and acute on chronic liver failure, have a high mortality rate. Recently a new artificial liver support system, named Molecular Adsorbent Recycling System (MARS), has been introduced in the clinical approach for selective therapeutic removal of water-soluble and albumin-bound toxins (1). The goal of the study has been to evaluate the cytokines variations and their clinical significance in patients with acute on chronic liver decompensation treated by MARS.

Patients and methods

Seventeen patients (aged between 18 and 60) with acute on chronic liver diseases (cirrhosis) were treated by MARS (TERAKLIN, Germany). All patients were in a transplant waiting list. The diagnosis was based on the standard examinations previewed by the National Protocol.

The indications to MARS treatment were: bilirubin >250 mm/L, encephalopathy (HE) stage II-III, serum creatinine (crs), >1.5 mg/dl. Patients with sepsis, pregnancy, severe coagulopathy, were excluded.

MARS treatment has consisted in 3 consecutive days treatment (6 hours each one) followed by 3 treatment one on the other day.

Before, during and after treatment, IL-6, TNF- α , bilirubin, liver function tests and renal tests were measured. Blood pressure was taken 3 times during treatments. The neurological status was verified before and after each treatment.

Results

The results are shown in fig. 1. IL-6 increased during each treatment while TNF- α significantly decreased (T Test - $p < 0.001$). This result was more evident in the first 3 days (continuous treatment), while during treatment in the alternative days, IL-6 was not significantly high. Bilirubin significantly decreased (pre treatment 560 ± 159 mmol/L range 340-720; post treat-

ment 421 ± 197.98 range 290-607), Creatinine decreased with respect to the pre treatment value ($p < 0.01$). Encephalopathy passed from stage III to stage II. Blood pressure was stable during treatment ($120/70$ mmHg ± 15). Four patients died for MOF. All of these patients were out of the protocol and treated with compassion intent. IL-6 and TNF- α had a controversial answer: IL-6 increased in 1 patient while did not increase in the other 3 ones. TNF- α increased in all 4 patients and never decreased. Severe pruritus disappeared in 3 patients (biliary cirrhosis) after 5 treatments.

Discussion

The Molecular Adsorbents Recycling System (MARS), is a device in which patient's blood is dialysed across an albumin-impregnated membrane against a recirculated albumin-containing solution. It seems to be effective in removing albumin-bound toxins, such as fatty acids, bile acids and bilirubin. Although the clinical experience with MARS is scarce, some pilot studies have reported its effectiveness in improving liver function and hepatic encephalopathy in patients with acute decompensation of chronic liver disease, and renal function in patients with hepatorenal syndrome type I. Data regarding MARS experience in acute liver failure and in primary graft dysfunction are encouraging but limited.

These results are evident because liver failure is a clinical syndrome that results from loss of functional liver cell mass below a critical level. It is a complex metabolic disorder associated with an accumulation of toxin, where cytokines play an important role. Cytokines in fact play a crucial role in liver diseases (2), and the monitoring of their levels may be an usefulness indicator of response to treatment. The cytokines control a wide variety of biological and pathological processes. It has been shown in models of inflammation, where several cytokines are produced, that specific blockade of their IL-1 or TNF- α or both results in a reduced severity of the disease. It is clear that IL-6 plays an important role in liver regeneration. In our experience, the massive detoxification induced by the MARS system, probably helps the hepatic cells to regenerate, increasing the IL-6 level. It is difficult

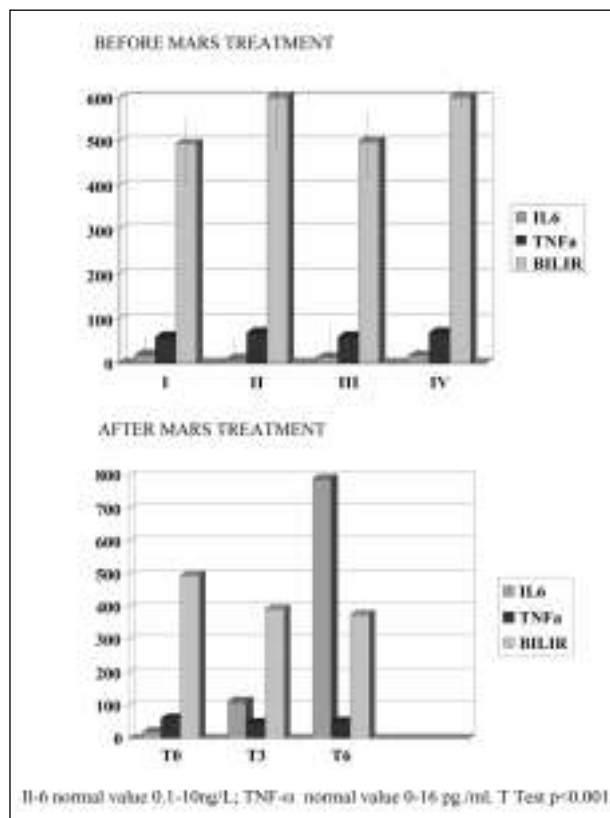


Figure 1. IL-6 and TNF- α level before and during mars treatment

anyway to demonstrated the MARS action on the cytokines behavior. IL-6 increased and TNF- α decreased in patients in which the outcome was much more better. In the 4 dead patients the cytokines level had different behavior.

It was a direct action, or an indirect answer? Difficult to say. Besides it is not possible to measure TNF- α and IL-6 level into the system, because the albumin used for treatment contains high quantity of these 2 cytokines. It is clear on the other hand, that liver regenerates after 6 treatments and cytokines levels should be monitoring as a predictive factor on the outcome.

Improvement of biochemical profile and liver synthetic functions, increasing of IL-6 and decreasing of TNF- α , due to MARS treatment are crucial in these patients improving the final outcome.

MARS seems to be safe and useful and our brief experience suggests its use on this kind of patients. The mortality can be high if the indications are wrong and the patient is already in a non recoverable (end-stage disease) status. Detoxification is an important

action to promote and favoring liver regeneration, but liver should have a sufficient reservoir to respond to the injuries.

Further studies will explain the significance of cytokines response after MARS treatment and their role on the liver regeneration after major injury.

Reference

1. Stange J, Mitzner SR, Risler T, et al. Molecular Adsorbent Recycling System: clinical results of a new membrane-based blood purification system for a bioartificial liver support. *Artif Organs* 1999; 23 (4): 319-30.
2. Burger D, Dayer JM. Cytokines, acute-phase proteins and hormones: IL-1 TNF- α production in contact-mediated activation of monocytes by T lymphocytes. *Ann NY Acad Sci* 2002; 966: 464-73.

Correspondence: Dr. Giovanni Ambrosino
Dip. Scienze Chirurgiche e Gastroenterologiche
Unità di Trapianto di Fegato
Università di Padova