The sooner the better

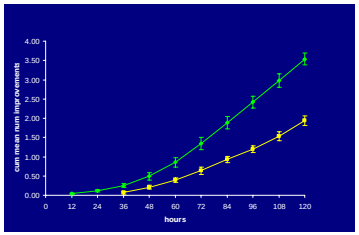
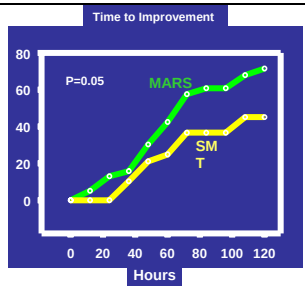
THE HE PUBLICATION: SUMMARY

The standard medical treatment for hepatic encephalopathy was first established more than three decades ago.
This trial is the first well designed randomized controlled study showing clear favourable effects of an extracorporeal liver support device as compared with SMT in cirrhotic patients with a deep HE.

The HE trial:

Primary Aim	Inclusion Criteria	Exclusion Criteria	Patients
Efficacy (Improvement Proportion), safety, and tolerability of albumin dialysis (MARS) in patients with advanced stages of HE Grade 3 and 4 and End Stage Liver Disease	ESLD with Hepatic Encephalopathy Grades 3 or 4 Informed Consent Obtained	• Bleeding within previous 24 hours • Hemodynamically unstable • Uncontrolled sepsis, Carcinoma • Hemodialysis or CRRT • Fulminant liver failure, post-liver transplant • Pulmonary edema, massive aspiration pneumonia • Active alcohol consumption • Portal vein thrombosis in patients with Hepatocellular	• 70 pat. (USA and 2 European) • Age 52.7 ± 10.9, 44% female, MELD 31 ± 10, CTP 12.7 ± 1.3, HE grade III 56%, HE grade IV 44% HE-assessment every 12 hours for 5 days (10 assessments per pat.) • Primary endpoint: Difference in improvement proportion (%) of HE between the two groups

The HE results:

1.- Mean improvement proportion (IP): MARS (34%) vs. SMT (18.9%) (P=0.044). IP : number of improved HE assessments in a patient (≥2 grade improvements from baseline) divided by the total amount of assessments done in this patient Responder : patients having at least one 2-grade improvement in HE anytime during the 5-day study period	
2.- HE improvement reached faster and more frequently in MARS group than in SMT group (P=0.045) Time to first improvement: time from randomization to the first assessment indicating improvement in HE of 2 grades.	
3.- Patients in the MARS group had signif. improvement in serum ammonia, bile acids, creatinine, branched chain/aromatic aminoacid ratio and blood urea nitrogen (BUN). Patients in the SMT group had an improvement in only bile acids levels.	

The HE Objections and……Comments:

There is no impact on survival: "*Mortality was not improved by MARS at all*" (Ferenci and Kramer's Editorial)	The trial was designed to assess the effect of MARS on HE and not the survival. "*It would have been a miracle to get differences on survival after a mean of 2.7 dialysis sessions in the MARS group*" (Professor Arroyo's Editorial)
"*The authors formulated 2 non validated and previously undescribed tools: "the improved proportion" (IP) and the "Hepatic Encephalopathy Scoring Algorithm" (HESA)*" (Ferenci Editorial)	This "*undescribed*" tools were accepted by the majority of the reviewers, and anyway were used in both arms; in patients receiving Standard Medical Therapy (SMT) or MARS. Moreover, The use of the HESA (an enhanced version of the West Haven criteria for HE) increased the accuracy of the HE assessments.
"*At the time of initialization of MARS, patients received standard of care (SOC) somewhat longer than in the SMT group . Therefore it is conceivable that prolonged exposure to SOC may account for the better IP in MARS*" (Ferenci and Kramer's Editorial)	"*…all patients had grade III-IV encephalopathy at randomization, an alternative possibility is that there were more patients with encephalopathy refractory to SMT in the MARS group*." (Professor Arroyo's Editorial)
Why there is not an equal number of patients in both arms (39 vs. 31)?	In a randomized trial is sometimes very difficult to achieve 50% in each arm specially when some hospital recruit few patients
Why 70 patients?	This is the number of patients we agreed with the FDA, based on their requests and on the need to have enough patients to reach statistical significance
Why did it take so long to get the paper published?	The authors were so confident about the quality of the study that they wanted to submit the paper only to the top medical journals (NEJM, The Lancet,…) which is a time consuming process.
Some patients showing HE are not eligible for MARS therapy because the risk of infection or complications associated with the treatment.	MARS is the treatment of choice to improve HE in patients with decompensated chronic liver disease, because MARS has proved to be more effective than the actual SMT with statistically significant difference. Therefore, patients not showing response to SMT could potentially be treated with MARS (The sooner the better).

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