Horizon Scanning report No. 15

Allogeneic bio-artificial liver support system

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Methods

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A full description of the methods used for the production of the present HS report can be found at www.agenas.it

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Limitations

This report is based on information available when the searches were made and does not contain data on subsequent developments or improvements of the evaluated technology. The observations made on effectiveness, safety or cost-effectiveness of the technology evaluated in the report are to be considered temporary.

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Declaration of Conflict of Interest

The authors declare that they will not receive either benefits or harms from the publication of this report. None of the authors have or have held shares, consultancies or personal relationships with any of the producers of the devices assessed in this document.

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Name of the technology / procedure: Allogeneic bio-artificial liver support system

Target population

The bio-artificial liver support system with human cells is proposed for adult patients with Acute Liver Failure (ALF), such as Acute Alcoholic Hepatitis (AAH), Acute on Chronic Liver Failure (AOCLF) and Fulminant Hepatic Failure (FHF).

Description of the procedure and technology

Extracorporeal liver support systems aim to prevent the manifestations of liver failure and bridge patients to liver transplantation or allow the recovery of native liver functions, avoiding in this way the transplantation in certain cases. They can be grouped into artificial (i.e., non-biological), if based on purely mechanical effects, or bio-artificial (i.e. cell-based), if they use living cellular components. In the past decades, several artificial and bio-artificial systems have been proposed and clinically tested for both ALF and AOCLF [Lee WM, 2012].

The artificial systems remove toxins by diffusion (haemodialysis), filtration (plasmaphaeresis), adsorption (haemoperfusion) and/or convection (haemofiltration) [Nevens F, 2012]. These systems have shown some limits related to the lack of the synthetic role, proper of the hepatic cells. Artificial systems include, for example, the extracorporeal albumin dialysis systems and the fractionated plasma separation and absorption systems.

Bio-artificial systems are designed to perform detoxification together with biotransformation and synthetic functions of biochemically active hepatocytes [Nyberg SL, 2012]. Bio-artificial systems use hepatic cells lines derived from animals (xenogeneic; usually porcine cells) or humans (allogeneic This HS report focuses on the extracorporeal bio-artificial liver support systems that use human hepatocytes.

Clinical importance and burden of disease

ALF is defined as a sudden loss of hepatic function in a person without pre-existing liver disease [Lee WM, 2012]. The most reliable signs of severe acute liver injury are the presence of coagulopathy and any degree of hepatic encephalopathy, the length of illness being considered anything ≤ 24 weeks. It may occur from diverse causes such as excessive alcohol consumption, medications overdose or individual reaction to specific drugs.

Specific forms of ALF are Alcohol Induced Liver Decompensation (AILD) and Fulminant Hepatic Failure (FHF). When ALF occurs in presence of underlying liver diseases, it is called AOCLF (e.g. in case of Acute On Chronic Hepatitis). AILD is a life-threatening disease precipitated by the recent ingestion of alcohol and can occur with or without chronic underlying liver disease. AAH is a form of AILD, characterised by inflammation and enlargement of the liver. Since 6 months abstinence from alcohol consumption is a prerequisite for liver transplantation, organ transplantation cannot usually be a solution for those patients. FHF is characterised by a rapid deterioration of the liver functions, altered mental state and coagulopathy in subjects with no pre-existing liver disease. Most frequent causes are, for example, drugs, toxin induced liver injuries, viral hepatitis. Standard of care includes liver transplantation.

The management of patients with ALF aims to prevent irreversible organ damage, while waiting for either liver recovery or transplantation. Patients will be treated through medication and/or treatments that control complications such as cerebral edema, circulatory dysfunction, infections, gastrointestinal bleeding or with liver transplant when no spontaneous recovery is possible. Standard of care for ALF patients includes medications and treatments such as pentoxifylline, corticosteroids, abdominal paracentesis, nutritional therapy, etc. typically given to these patients. If standard medical therapy fails to improve the condition of the patient, liver assist devices may be a treatment option for bridging the patient either to transplantation or native liver recovery. In patients with contraindications to transplantation, liver assist devices could be the only treatment option to attempt recovering hepatic functions [T. Kantola, et al. 2011]. In our country we do not have a monitoring system specific for ALF. As mentioned above, one important cause of ALF are viral hepatitis. Indeed about 0.5 % of cases of hepatitis A will result in ALF and cause-related mortality reaches up to 2.1% in adults over 40 years [Tosti ME, 2008]. The most recent epidemiological data attest an incidence rates of about 0.8 cases/100,000 inhabitants [SEIEVA, 2012]. Hepatitis B, is symptomatic in 30-50% of adults, with a case-fatality of approximately 1%. In Italy, incidence rate in 2012 was 0.85 cases/100,000 inhabitants, with a 1% of general population seropositive for the HBV6 [Hyams KC.1995] Data coming from studies performed in the nineties on prevalence of HCV infection in Italy, show variable rate from 3.9% to 16.2% [SEIEVA, 2012]. Recent EU data show that Italy has the highest prevalence of HCV positive people in EU countries [ECDC, 2010]. Incidence rate at 2012 was 0.25/100,000 inhabitants [Hatzakis A, et al. 2013]. Italian epidemiological data related to drug-induced hepatitis are derived almost exclusively from analysis of spontaneous reports made within the services of pharmacovigilance, showing that more than 16% of ALFs is caused by drugs [SIT, 2013]. In Italy liver diseases are the leading cause of death in the age group between 35 and 44 years and the third in the range between 45 and 54 years [ECDC, 2010]. In 2008 the MDC - Major Diagnostic Categories 7 “Malattie e disturbi epatobiliari e del pancreas” equal to the 5% of all Italian Regions hospital services expenditure [AISF, 2011]. As regard to transplantations, at the beginning of January 2012, 2181 patients were on the waiting list for liver transplantation. From January 2012 to December 2012, there was a total of 986 transplantations. Patients still on the waiting list were 973 (at the end of 2012). The deaths occurred during the wait were 174, while 48 patients dropped out for other reasons. The average wait for a liver transplant is 2 years and the death rate during the wait is 8 %. From 1st January to 30th April 2013, liver transplants were 976: 909 of total liver and 67 of liver’s split [SIT, 2013].

Products, manufacturers, distributors and approval

We identified only one bio-artificial liver support system that uses human hepatocytes: the ELAD System manufactured by Vital Therapies, Inc. The first versions were developed by VitaGen, Inc. The system received some technical improvements after the company was acquired by Vital Therapies, Inc. in 2003. Since 2006 no relevant changes have been made. The ELAD system is intended to stabilise liver function in patients with ALF by processing toxins and synthesising proteins, possibly enabling a bridge to transplant or

liver recovery [Vital Therapies website].
The ELAD system is subjected to different regulations in different countries. We report below the countries in which ELAD trials are ongoing and the regulating body in charge of approval:

- In Europe: the ELAD system is regulated by the European Medicines Agency (EMA) as a Combined Advanced-Therapy Medicinal Product (ATMP); in 2013 the manufacturer received the Orphan Medicinal Product Designation by the EMA for the cells used as active ingredient of the ELAD system for the treatment of ALF [Vital Therapies website]. As a Combined ATMP, CE mark will not be mandated for the associated extracorporeal support system (bedside units and dispensable sets).
- In the USA: the ELAD system is regulated by the FDA's Center for Biologics Evaluation and Research (CBER) as a combination biologic product; in 2013 the manufacturer received the FDA's Orphan Designation for the use of immortalised human liver cells to treat ALF [Vital Therapies website].
- In China: the ELAD system is regulated as a medical device and a regulatory submission is pending.

The ELAD system comprises four hollow fibres cartridges mounted on a bedside unit that embeds also an ultrafiltrate generator and glucose, oxygen and temperature control units. The cartridges contain immortalised human liver-derived cells (C3A cells). The patient's plasma flows between the cells through the hollow fibres in the cartridges, allowing the cells metabolise toxins (such as ammonia and bilirubin) and synthesise proteins and other liver specific products. Treated plasma ultrafiltrate is then filtered, reconstituted with blood cells and returned to the patient via the central venous line. Therapy is expected to consist of a single session of continuous treatment lasting between 3 and 10 days, as determined by the treating physicians.
The bedside system, disposables, and cartridges are sourced from different medical device suppliers while the cells used are proprietary: they are grown in the cartridges at the manufacturer's facility, stored and shipped worldwide. Once incorporated into the bedside unit, a set of cartridges enables continuous treatment for up to 17 days [Vital Therapies website].

Product name [Manufacturer]	Distributor	CE Mark	RDM	FDA
ELAD System [Vital Therapies, Inc].	None for Italy	n/a*	☐	☑**

* n/a = not applicable; the manufacturer received the Orphan Medicinal Product Designation by the EMA.

** FDA's CBER Orphan Designation.

Setting

The ELAD system must be used in the healthcare centres in which an Intensive Care Unit (ICU) is available.

☐ Home	☑ Hospital	☐ Outpatients
☐ Accident and Emergency	☐ Other:	

Roll out in Italy

The ELAD system is in use exclusively within clinical trials (now entering Phase 3) in several centres based in the United States, United Kingdom, Germany, Spain and Australia. There are no Italian centres involved in the trials. The manufacturer stated that commercial launch in Italy has been planned between 2016 and 2018.

☑ Pre-marketing	☐ On the market for 1-6 months	☐ On the market for 7-12 months
☐ On the market for more than 12 months	☐ Not identified	

Comparators

The allogeneic bio-artificial liver support system is proposed in addition to standard therapy. Such standard therapy consists in various paths of medical management but has not been extensively studied and remains poorly defined [Lee WM, 2012]. Within the ongoing trials on the ELAD system, standard-of-care is defined as per the American Association for the Study of Liver Disease (AASLD) and European Association for the Study of the Liver (EASL) guidelines (O'Shea et al. 2010, Lee WM at al. 2011, EASL, 2010). Other support systems and therapies that may serve as a bridge to liver transplantation or facilitate recovery in the defined target population, should be considered as comparators of the technology being assessed. Such systems are the Molecular Adsorbent Recirculating System (MARS), the Liver Dialysis Unit (former BioLogic-DT System), hemoperfusion systems, as well as all the extracorporeal cell-based bio-artificial liver systems that use xenogeneic cells (e.g. HepatAssist, Modular Extracorporeal Liver Support).

Effectiveness and safety

We carried out searches on EuroScan database (18th October 2013) looking for HS reports on bio-artificial systems using human cells and did not find any report. Further searches were done on MEDLINE, Embase and the Cochrane Library (4th November 2013), looking for studies on effectiveness and safety of the ELAD

system, published in Italian or English. We identified 411 records. They were all screened by reading title and abstract and 13 of them were selected for full text reading. After full text reading they were all excluded as not being on the technology at stake (e.g. the latest configuration of ELAD) or not in Italian or English language.
We run searches on the ClinicalTrial.gov database (17th October 2013) and identified 8 registered clinical trials on the ELAD system (Table 1).
Two Phase III trials are registered as "not yet recruiting"; they are on the use of ELAD for FHF patients and for AAH/ALF patients; completion is estimated by the end of 2017 and 2015, respectively. One Phase III trial is registered as "recruiting" and it is on the safety and efficacy of ELAD in AAH patients; it is estimated to be completed in 2014. One Phase II trial, started in 2009, and a Registry, started in 2010, are registered as "withdrawn" and "terminated" respectively. Three trials are registered as "completed" but we did not identify any results for them. The manufacturer confirmed that results have not been published as full articles on peer-reviewed journals, only abstracts of oral/poster communications are available (Table 2).
Hillebrand D.et al. 2010 is an oral presentation of results from a multicentre Phase 2 open label concurrent control study (VTI – 201, registered on ClinicalTrials.gov as NCT00771446 held in 2008-2009) to evaluate the safety and efficacy of ELAD in 18 adult Acute on Chronic Liver Failure patients. According to authors Standard Medical Therapy (SMT) plus ELAD in these patients improved transplant free survival at 30 and 90 days and overall survival at, it was safe and well tolerated.
Teperman L. 2012 and 2013 are two presentations of results from a Phase 2 multicenter Clinical Trial (VTI – 206, registered on ClinicalTrials.gov as NCT00973817 held in 2009-2011) evaluating the efficacy and safety of ELAD in acute alcoholic hepatitis (AAH) or acute decompensation of cirrhosis (non-AAH). Adults with AAH or non AAH and Model for End-Stage Liver Disease (MELD) of 18-35 were randomised to Standard Medical Therapy (SMT) plus ELAD or SMT. Author states that SMT plus ELAD was well tolerated and improves 90-day survival in AAH patients. Transplant rates were not affected. ELAD subjects, but not SMT subjects, had significant reductions from baseline in total bilirubin.
Duan Z, et al 2007 is a presentation abstract about results of a clinical trial (VTI 301) held in China on adult AOCLF patients. Authors concluded that ELAD appeared to be effective in bridging AOCLF patients to recovery. Duan Z, et al. 2010 shows results of a three years follow up of patients involved in the above study and aimed at evaluating risk of tumour formation at 3 years and rate of transplant free survival. Authors highlights that there was a statistically significant 3 years transplant free survival advantage in the ELAD group and there was no evidence of an increased risk of tumour formation in this patients population.

Potential benefits to patients

The use of the ELAD system is intended to increase survival and/or reduce morbidities (e.g. hepatic encephalopathy, immunological risk) in the target population.

☑ Mortality reduction or increased survival	☑ Reduction of the morbidity	☐ Improved quality of life (patient/users)
☐ Improved patient monitoring	☐ Other:	☐ Not identified

Cost of the technology / procedure

As the ELAD is always proposed in addition to SMT, its introduction will result in new costs. Nonetheless we cannot quantify exactly the cost per each ELAD treatment, as its costs have not yet been evaluated by producer. At the time of writing (November 2013) manufacturer stated there is a protocol for tracking economic data in three ongoing clinical trials.

☐ Increased costs compared to alternative treatments	☐ Increased costs due to increased demand	☐ Increased costs due to the required investments
☐ New costs	☐ Other:	☑ Not identified

Potential structural and organisational impact

Structural impact

There are no relevant structural issues. No special plant provisioning is required and equipment dimensions and weight are compatible with general operational activities. The manufacturer stated that most of the equipment required for the therapy with the ELAD system is provided as part of the system (these include the cartridges, the bedside unit and various disposables, such as tubing and ultra-filtrate generators). However some material and solutions (e.g., saline, heparin, albumin) must be provided by the hospital pharmacy.

☑ Increase in requirement of instruments	☑ Always be used	☐ Can be used only under specific circumstances
☐ Decrease in requirement of instruments	☐ Other:	☐ Not identified

Organisational impact

When the hospital receives the ELAD cartridges they must be unpacked by a specialist sent by Vital Therapies on site, placed on the bedside unit and flushed with saline to be used on patient. The ELAD specialists team (three specialists for each procedure - 8 hours shifts - for 5 days therapy) is responsible for continuous 24-hours on site operation and management of the ELAD System. Specialists, who typically have a prior clinical experience as intensive care nurses or perfusionists, go through an in-house certification process where they are trained to manage ELAD prior and during therapy. The manufacturer is planning to implement training for the users upon commercialisation, but no cost data have been disclosed.

☑ Increase in the number of procedures	☑ Re-organisation required	☑Training required for users
☐ Reduction in the number of procedures	☐ Other:	☐ Not identified

Conclusions

An allogeneic bio-artificial liver support system may represent a suitable bridge therapy to help target population in surviving free of immunological risks and other co-morbidities. Given the paucity of liver donors, the severity of the condition(s), and the lack of optimal alternative treatments, we acknowledge that such technology could save several lives.

The use of human hepatic cells within the ELAD system granted the Orphan Designation for ALF by the EMA and FDA respectively, and Phase III trials are currently ongoing and will be completed after 2015. No final statements can be made about the effectiveness and safety of the ELAD System, as the results of completed studies have not been published, in details and as full article, on peer reviewed journals. Abstracts of conferences presentations showed that for AOCLF and AAH patients, in phase 2 clinical trials, ELAD seems to be safe and effective.

At now, the introduction and use of the technology in clinical practice is limited to the regulatory status of the technology itself and should be managed exclusively within tough evidence-generation frameworks.

Future prospects

The manufacturer is currently working on improvements to user-friendliness and system size. Producers say that data from ongoing Phase 3 trials will be available from 2015 and regulatory approval from FDA will be sought in 2016 and EMA will be sought in 2017.

Table 1: Summary of the registered studies on ELAD system identified on ClinicalTrials.gov

Trial number: "Official title"	Device used	Condition	Purpose	Intervention model	Arms		Enrolment [patients]	Date (Start – Completion)
					Experimental	*Active comparator*		
NOT YET RECRUITING								
NCT01829347 Other study identity name: VTI-210 A Randomized, Open-Label, Multicenter, Controlled Study to Assess Safety and Efficacy of ELAD in Subjects With Acute Alcoholic Hepatitis (AAH) Who Have Failed Steroid Therapy Phase 3	ELAD	Acute Alcoholic Hepatitis (AAH)	The purpose of this study is to determine if treatment with the ELAD system is safe and effective in patients with acute alcoholic hepatitis	Parallel Assignment	ELAD plus standard of care	Predefined treatment for AAH complications	Estimated: 120 Both genders 18 Years and older Patients where the steroid treatment is not working.	Dec. 2013 – Nov. 2015 (estimated)
NCT01875874 Other study identity name: VTI-212 A Randomized, Open-Label, Multicenter, Controlled Study to Assess Safety and Efficacy of ELAD in Subjects With Fulminant Hepatic Failure (FHF) Phase 3	ELAD	Acute Liver Failure (ALF) Fulminant Hepatic Failure (FHF)	This study is developed to determine if ELAD helps survival (up to 28 days) in subjects that have fulminant hepatic failure (FHF) which is acute liver failure with no pre-existing liver disease.	Parallel Assignment	ELAD plus defined treatment for common problems that accompany FHF.	Standard of care plus defined treatment for common problems that accompany FHF.	Estimated: 126 Both genders 18 – 65 Years	Dec. 2013 –Sept . 2017 (estimated)
RECRUITING								
NCT01471028 Other study identity name: VTI-	ELAD	Acute Alcoholic Hepatitis	The objective of the study is to evaluate safety and efficacy of ELAD with respect to overall survival (OS)	Single Group Assignment	ELAD plus standard of care	Standard of care	Both genders 18 Years and older	Feb. 2013 –Aug. 2014 (estimated)

208 A Randomized, Open-Label, Multicenter, Controlled Study to Assess Safety and Efficacy of ELAD in Subjects With Alcohol-Induced Liver Decompensation (AILD) Phase 3			of subjects with a clinical diagnosis of alcohol-induced liver decompensation up to Study Day 91.Secondary objectives are to evaluate the proportion of overall survival at Study Days 28 and 91. An exploratory objective is to evaluate the ability of ELAD to stabilize liver function.						
COMPLETED									
NCT00771446 Other study identity name: VTI-201 Safety & Efficacy of the Extracorporeal Liver Assist Device (ELAD) System in Patients With Hepatic Insufficiency Phase 1 Phase 2	ELAD	Acute on Chronic Hepatitis (AOCH)	To provide evidence that (1) subjects treated with ELAD have a higher 30-day transplant-free survival in subjects with AOCH than those not treated with ELAD, and (2) it is safe when used for 3 to 10 days of treatment.	Parallel Assignment	Medical therapy for acute liver failure plus the ELAD	Standard medical therapy (i.e. conventional therapy for AOCH determined to be clinically appropriate by the treating physician)	N=18 Both genders 19- 69 Years	Oct. 2008 – Apr. 2009 (for primary outcome measures) Certification or Request for Extension to Delay Results Received: Jul. 24, 2012	19 Years to 69
NCT00973817 Other study identity name: VTI-206 Efficacy and Safety of the Extracorporeal Liver Assist Device (ELAD) in Acute on Chronic Hepatitis (SILVER) Phase 2 Phase 3	ELAD	Acute On Chronic Hepatitis (AOCH)	The purpose of this study is to investigate the safety and efficacy of the use of ELAD in patients with diagnosed AOCH including AAH.		ELAD plus standard of care	Standard of care for AOCH including medications and treatments for AH (pentoxifylline, corticosteroids, etc., if indicated)	N=62 Both genders 18-67 Years	May 2011- Apr. 2011 (for primary outcome measure) Certification or Request for Extension to Delay Results Received: July 24, 2012	
NCT00030225 Other study identity name: CR-202	ELAD – former configuration	Acute Liver Failure (ALF)	The purpose of this study is to determine if treatment ELAD is beneficial to patients in ALF either as a bridge to liver transplant or bridge	Single Group Assignment	ELAD	Standard of care for patients with fulminant	N= 19 Both genders 18-50 Years	Jan. 2002-Feb. 2003	

Phase 2 Evaluation of the Vitagen Extracorporeal Liver Assist Device (ELAD) System in the Management of the Patients With Fulminant Hepatic Failure Phase 2			to native liver recovery			hepatic (liver) failure		
WITHDRAWN								
NCT00832728 Safety and Efficacy of the Extracorporeal Liver Assist Device (ELAD) In Patients With Fulminant Hepatic Failure (FHF) Phase 2	ELAD	Fulminant Hepatic Failure (FHF)	Primary Outcome Measures: The effect of ELAD therapy: 1) as a bridge-to-transplant/recovery and 2) on 30-day transplant-free survival in subjects with FHF [Time Frame: 30 day] . To assess its safety when used for a minimum of 3 days or up to a maximum of 30 days of treatment [Time Frame: 30 day]	Parallel Assig nment	ELAD plus standard of care	Standard of care	N=62 Both genders 10-65 Years	Marc 2009- Sept 2011
ERMINATED								
NCT01452295 Registry Protocol for Tracking the Incidence of Transplant, the Incidence and Type of Cancer, and Survival Rate of Subjects Participating in Protocol VTI-206	ELAD	Acute on chronic (AOCH) hepatitis; Acute alcoholic hepatitis (AAH)	As hypothetical risk exists that, over an extended period of time, there may be an increased incidence of tumour in subjects treated with ELAD. This VTI-207 is designed to follow subjects, both treated and control, for five years after their completion of study participation in protocol VTI-206 to gather information relating to the incidence of liver transplant, the incidence and type of cancer (if any), and survival.	Parallel Assig nment	ELAD	Standard of care	N=62 Both genders 10-65 Years	Jun. 2010 – Sept. 2012

Table 2: Description of the abstracts of oral communication and posters

Ref.	Description	Patients	Reported results (by the study authors)
Teperman L., 2012	Clinical Trial VTI - 206 is multicenter, phase 2, randomized, controlled study evaluating ELAD in acute alcoholic hepatitis (AAH) or acute decompensation of cirrhosis (non-AAH). Endpoints: survival at 30 & 90 days and median time to progression (TTP) defined as a MELD increase of >5 points, transplant or death.	N=62 Age: 18-35 years	Standard Medical Therapy plus ELAD was well tolerated and numerically improved 90-day survival in acute alcoholic hepatitis (AAH) subjects. Transplant rates were not affected. A sufficiently powered, randomized, controlled trial in an AAH population is currently underway. Mean ELAD treatment was 93 (24-144) hours. 90-day OS numerically favored AHH subjects in the ELAD group (9/13 vs 7/16, p=0.27). Non –AAH subjects showed the opposite trend (1/6 ELAD vs 6/10 SMT). Liver transplant rates were similar with ELAD (2/19) and SMT (4/26).
Teperman L., 2013	Same study as the above (VTI – 206)	Same population as the above	ELAD subjects but not SMT subjects had significant reductions from baseline in total bilirubin during ELAD therapy (days 1, 2, 3 and 4). Mean reduction from baseline for ELAD subjects was 20% at days 3 and 4 p<0.01) while SMT subjects had a mean increase of 4% and 8%, respectively. Categorical analysis based on 10% threshold change from baseline total bilirubin showed significant differences between ELAD and SMT AAH subjects on days 1-4 (p<0.01).Changes in sodium and creatinine were also evaluated.
Duan Z, Xin S, Zhang J, et al, 2010	Clinical Trial VTI 301 – Determine 3 years Transplant free survival and tumor incidence in a controlled study of safety and efficacy of ELAD in in AoCLF patients in China.	N=49 Age: not declared	Three (3) years follow up of subjects enrolment in a clinical trial of ELAD in ACLF patients in CHINA confirmed that ELAD gives a statistically significant 3 years transplant free survival advantage compared with standard of care alone. There was no evidence of an increased risk of tumor formation in this patients population.
Duan Z, Zhang J, Xin S, et al, 2007	Clinical Trial VTI 301 – Details of a first use of ELAD in ACLF patients .	N=90 Age: mean 39,6 ±9.9 (ELAD group) - mean 39, 6 ±11.6 (Control)	The study showed a 30 day transplant free survival of 47% in controls and of 86% in the treated group (p= 0.004). Biochemical improvement supported the increased survival in the treated group. Thrombocytopenia was the only statistically significant safety issue. Platelets dropped in 28% of ELAD patients vs 0% in control group, but it could be managed by platelet transfusion and ELAD discontinuation. Results were on 54 patients (19= controls and 35=elad). ELAD is safe and there is statistically significant transplant free survival advantage for the ELAD treated patients. The technology appears to be effective in bridging patients with Acute on chronic liver disease to transplantation.
Hillebrand DJ, Frederick RT, Williams WW, et al, 2010	Clinical Trial VTI 201- Multicenter phase 2 open label concurrent control study. Efficacy endpoints included (transplant free survival) and overall survival at 30 and 90 days.	N= 18	ELAD+ SMT in ACLF patients improves Survival at 30 and 90 days. It is safe and well tolerated. ELAD treatment ranged from 36 to 240 hours. In the SMT+ELAD group 23% vs 0% of patients achieved 30-day transplant free survival, while there was no difference in the 30-day overall survival (SMT+ELAD 46% vs SMT 50%). 90 days overall survival and transplant free survival were both improved in the ELAD group. The rate of liver transplantation was higher for SMT patients (75%) vs ELAD (23%). ELAD was well tolerated. Of 39 SAEs reported (SMT+ELAD= 32, SMT=7) none were unexpected, and in 2 patients they were thought to be related to ELAD.

Evidence searches

Searches of the databases were carried out on 4th November 2013 according to the following criteria. Time: January 2000 to now; Languages: English/Italian; Patients: Any (humans).

We used the following keyword to indicate:

- ***the technology of interest:*** *bio artificial liver therapy, bio artificial liver AND allogeneic* therapy, bio artificial liver*+human cells based therapy, extracorporeal liver assist system, extracorporeal liver assist device, bridge therapy for liver transplantation.*
- ***the pathologies of reference:*** *Acute Liver Failure, Acute on Chronic Liver Failure, Fulminant Liver Failure, Liver Transplantation, Acute alcohol Hepatitis, Liver cirrhosis.*

Bibliography

AISF, Associazione Italiana per lo Studio del Fegato. Epidemiologia delle epatopatie acute e croniche in Italia, Febbraio 2007.

AISF, Associazione Italiana per lo Studio del Fegato. Libro Bianco, 2011.

Duan Z, Xin S, Zhang J, You S, Millis JM. 3-year follow up of acute-on-chronic liver failure (ACLF) subjects in a randomized, controlled, multicenter trial of the ELAD Bioartificial Liver Support System in 49 Chinese subjects reveals significant transplant-free survival (TFS) benefit. Hepatology 2010; 52:S1:1089.

Duan Z, Zhang J, Xin S, Chen J, He D, Brotherton J, Maxwell K, Millis M. Interim results of randomized controlled trial of ELAD™ in acute on chromic liver disease. Hepatology, October 2007; AASLD Abstracts, 274A.

ECDC - European Centre for Disease Prevention and Control. Hepatitis B and C in the EU neighborhood: prevalence, burden of disease and screening policies. Stockholm: ECDC; 2010.

European Association for the Study of the Liver (2012). EASL Clinical Practical Guidelines: Management of Alcoholic Liver Disease. Journal of Hepatology, 57, 399-420.

Hatzakis A, Van Damme P, Alcorn K, Gore C, Benazzouz M, Berkane S, et al. The state of hepatitis B and C in the Mediterranean and Balkan countries: report from a summit conference, J Viral Hepat. 2013 Aug; 20 Suppl 2: 1-20.

Hyams KC, Risks of chronicity following acute hepatitis B virus infection: a review. Clin Infect Dis 1995;20:992-1000

Hillebrand DJ, Frederick RT, Williams WW, Brown Jr. RS, Napotilano LM, Te HS, Millis JM, Ashley RA, Pockros PJ. Safety and Efficacy of the extracorporeal liver assist device (ELAD) in patients with acute on chronic liver failure. Journal of Hepatology 2010;52:S323-S324.

Kantola T, Ilmakunnas M, Koivusalo AM, Isoniemi H, Bridging therapies and liver transplantation in acute liver failure, Scandinavian Journal of Surgery 100: 8–13, 2011.

Lee WM, Stravitz RT, Larson AM. Introduction to the revised American Association for the Study of Liver Diseases Position Paper on acute liver failure 2011, Hepatology 2012; 55:965.

Lee WM, Recent developments in acute liver failure. Best Pract Res Clin Gastroenterol. 2012 Feb;26(1):3-16.

Lee WM, Larson AM, Stravitz T. AASLD position paper: the management of acute liver failure: update 2011. Baltimore (MD): American Association for the Study of Liver Diseases; 2011 Sep. 26 p.

Nevens F, Laleman W. Artificial liver support devices as treatment option for liver failure. Best Pract Res Clin Gastroenterol. 2012 Feb;26(1):17-26.

Nyberg SL. Bridging the gap: advances in artificial liver support. Liver Transpl. 2012 Nov;18 Suppl 2:S10-4.

O'Shea, RS, Dasarathy, S, & McCullough, A. J (2010) AASLD Practice Guidelines For Alcoholic Liver Disease. Hepatology, 51(1), 307 - 328.

SEIEVA, Sistema Epidemiologico Integrato dell'Epatite Virale Acuta at National Institute of Health, 2012, http://www.iss.it/seieva/ (accessed on 12th November 2013).

SIT, Sistema Informativo Trapianti https://trapianti.sanita.it/statistiche/home.asp (accessed on 12th November 2013).

Teperman L. 2013 “Bilirubin Improvement Correlates with 90-Day Survival with Use of the ELAD® System in a Randomized, Controlled Study of Subjects with Acute Alcoholic Hepatitis or Acute Decompensation of Cirrhosis” ATC Abstracts - Abstract number: 147.

Teperman L. 2012 “A Phase 2b Study of Safety & Efficacy of a Human Cell-Based Biological Liver Support System (ELAD®) in Subjects with Acute-on-Chronic Hepatitis (AOCH) Due Either to Acute Alcoholic Hepatitis or Acute Decompensation of Cirrhosis” Oral presentation at the 18th Annual International Congress of the International Liver Transplantation Society - 2012.

Tosti ME, Spada E, Romano L, Zanetti A, Mele A, group Sc. Acute hepatitis A in Italy: incidence, risk factors and preventive measures. J Viral Hepat 2008;15 Suppl 2:26-32.

Vital Therapies website http://vitaltherapies.com (accessed on 4th November 2013).

Glossary

AAH: Acute Alcoholic Hepatitis

ALF: Acute Liver Failure

AOCLF: Acute on Chronic Liver Failure

AOCH: Acute on Chronic Hepatitis

CRD: Centre for Reviews and Dissemination

ELAD: Extracorporeal Liver Assist Device

EMA: European Medicine Agency

FDA: Food and Drug Administration

FHF: Fulminant Hepatic Failure

MELD: Model for End-Stage Liver Disease

RDM: Medical Device Repertory

SMT: Standard Medical Therapy