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Extracorporeal photopheresis and liver transplantation: our experience and preliminary data

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Table 1. Clinical features of LT recipients in avoiding CI protocol.

	ECP ***(n=90)***	**NO ECP** ***(n=12)***	**p**
Age (years) n±DS	48,8±10,9	51,8±11,5	<0,001
Gender M/F	65/25 (72/28)	10/2 (83/17)	0,41
MELD at LT n±DS	15,7±6,8	14,3±9,8	0,53
D-MELD n±DS	920±513	1026±718	0,53
HCC Y/N	24/66 (27/73)	6/6 (50/50)	009
Donor age n±DS	59,2±19,7	74±15,2	0,014
Patient survival 1 year (%)	98,8	100	ns
Patient survival 5 years (%)	70,8	83,3	
Mean follow up time (years) n±DS	5,7±0,7	7,9±1,0	

Table 1 bis. Clinical features of LT recipients in avoiding CI protocol with at least 6 ECP sessions in the ECP group.

	ECP group (n=43)	**NO ECP group (n=57)**
Recipient age in years n (range)	50,8 (28-83)	48 (16-69)
Donor age in years n (range)	57,3 (18-83)	64,1 (15-88)
MELD at LT n (range)	16 (3-35)	15 (4-44)
D-MELD n (range)	892 (225-1840)	954 (217-3280)
Living at 2017 %	88,3	87,7
Mean follow-up time in days n (range)	2826 (199-4778)	2652 (196-5292)

Table 2. Donor and recipient clinical features of AB0-incompatible LT treated with ECP

Recipients (n=12)	
Age (years) mean n (range)	55 (38-63)
Gender M/F n (%)	7/5 (58/42)
MELD at LT n (range)	13 (11-18)
D-MELD n (range)	863 (608-1079)
Hospital stay (days) n (range)	27 (13-70)
1 year graft survival (%)	100
5 years graft survival (%)	75
Follow up (years) n (range)	7,8 (2,0-12)

Donors (n=12)	
Age (years) mean n (range)	55 (17-83)
Gender M/F n (%)	6/6 (50/50)

Table 3. LT clinical features stratified by ECP study group.

	HCV positive recipients (n=355)				
	ECP group (n=261)		**NO ECP group (n=94)**		**p**
DONOR AGE YEARS (range/n)	16-88	63,1	4-87	56,8	0,002
RECIPIENT AGE YEARS (range/n)	27-68	53,6	15-67	52,8	0,41
MELD n	±4.4	12,6	±4.6	12,6	0,97
D-MELD n	150-2336	790	60-1944	688	0,01
LIVING IN 2017 (%)	191	73	55	58	
HOSPITAL STAY (days)	7-240	23	3-100	21	0,16
1 year graft survival (%)		90,4		79,8	
5 year graft survival (%)		73,9		67,9	
HCV RECURRENCE (n)	86	death 38	13	death 9	

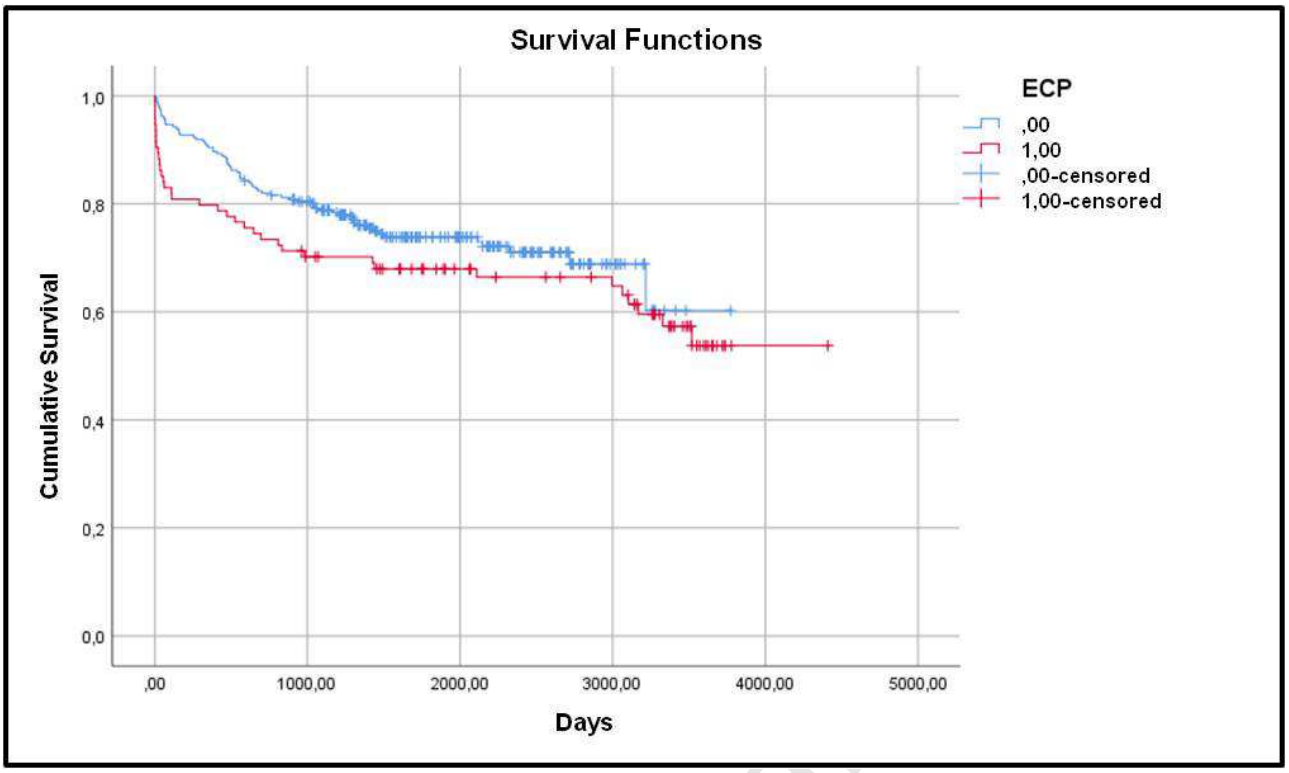

Image 1. The survival trend in the ECP group (blue line) and the control group (red line).

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Introduction

Extracorporeal Photochemotherapy/Photopheresis (ECP) is considered an immunomodulating therapy with several potential clinical applications. ECP was initially developed by Edelson et al. (1) as a treatment for cutaneous T-cell lymphoma (CTCL). In 1988, the use of ECP was approved by the U.S. Food and Drug Administration as standard therapy for the treatment of patients with advanced refractory CTCL (2). Later, ECP was used in the treatment of several autoimmune T-cell-mediated diseases such as pemphigus vulgaris (3, 4), systemic sclerosis (5, 6), rheumatoid arthritis (7, 8), Crohn's disease (9, 10) and multiple sclerosis (11). Moreover, ECP was introduced for the treatment of solid organ allograft rejection (12, 13, 14, 15, 16), acute and chronic graft versus host disease (GvHD) post-allogenic hematopoietic stem cell transplantation (HSCT) refractory to the conventional immunosuppressive therapy (17, 18, 19, 20, 21, 22, 23). ECP consists of three principal steps: there is the lymphomonocyte collection (through a temporary peripheral venous access), then these autologous peripheral blood leukocytes are treated ex-vivo with 8-methoxypsoralen (8-MOP) and UVA light, and finally reinfusion of the blood product treated. There is growing evidence in the field of heart, lung and kidney transplant supporting the use of

ECP as a potential treatment for graft rejection (24). Moreover, the safety and tolerability of ECP have spurred various authors to investigate its potential application in either tolerance induction or maintenance therapy after organ transplantation.

In 2001, at the beginning of our experience we explored the efficacy of ECP in the treatment of recalcitrant graft rejection and the results suggested that ECP may represent a valuable alternative to treat graft rejection in selected recipients. As a consequence ECP was implemented in the prophylaxis of allograft rejection in liver transplantation (LT) and three main fields of application in the immediate postoperative period and related protocols were identified: avoiding a calcineurin inhibitor (CI) protocol, an AB0-incompatible protocol and a HCV protocol.

Avoiding a CI protocol

The first field of ECP application was the so-called "Avoiding CI protocol". In the immediate postoperative period, immunosuppression is at its peak while graft and patient recovery are incomplete. Therefore, the risk of developing CI adverse effects is at the highest level at this stage. Recently, we reported on the feasibility of a peri-operative ECP-based immunosuppressive regimen to delay CI introduction in 18 high-risk LT recipients in order to better manage CI-toxicity without jeopardizing the graft and patient survival rate (25, 26).

Criteria for inclusion of patients at risk of post-LT renal impairment and neurological complications have been defined as having one or more of the following risk factors: a calculated glomerular filtration rate (cGFR) of 50 ml/min at transplantation; severe ascites at transplantation; a history of more than one hospitalization for encephalopathy within one year before transplantation and/or one hospitalization within one month before transplantation, and age > 65 years. All LT recipients who were HCV negative and showed one or more of these criteria were screened preoperatively to assess compliance with the current protocol. A written consent was necessary for enrollment (parent or legal guardian for "UNOS status 1" patients). The retrospective study design included a control group (non-ECP patients) with the same inclusion criteria but standard dose immunization

Standard CI-based immunosuppression was defined as full-dose CI administered from post-transplant day 1 (cyclosporine A CyA 10 mg/kg/day and tacrolimus TAC 0.1 mg/kg/day) in association with either antimetabolites or steroids or both. The immunosuppressive protocol in the study group consisted of induction with anti-CD25 monoclonal antibodies (basiliximab, Simulect^{TM}, Novartis, Basel, CH) 20 mg i.v. on post-transplant day 1 and 4; mycophenolate-mofetil (MMF) or AZA at a dosage of 2 g/day and 1 mg/kg/day, respectively; steroids (6-methyl-prednisolone) 10 mg/kg on graft reperfusion tapered within the third post-transplant month. CI were introduced as clinically indicated with the goal of sparing or delaying CI introduction in order to avoid CI toxicity.

All the LT recipients included in the avoiding CI protocol staggered the CI introduction from postoperative-day (POD) #4: in 6 (33.3%) patients, CI was introduced after the POD #8 to an average of 22 days (range 12-55 days), while one patient remained on a complete CI-free regimen. These data were confirmed in a subsequent cohort of 24 consecutive high risk LT recipients.

Until 2017 we continued to apply this protocol and the data obtained confirmed the preliminary results. During this period the “avoiding protocol” was applied to 88 HCV-negative liver transplant recipients (88%). This group was divided into two subgroups: 80 patients delayed the introduction of CI for 4 days at least, with a recipient age of 49 years on average (range 16-83 years), donor age 59 years on average (range 15-85), MELD 16 (range 3-44), D-MELD 920 (range 217-3280), with follow-up for 2678 days (range 196-5292 days). Among them 8 patients incidentally died of lung cancer, esophageal cancer, alcoholic relapse, HCC-recurrence, pulmonary sepsis, ischemic-type biliary lesions (ITBL), cholangiocarcinoma, post ERCP (endoscopic retrograde cholangio pancreatography) and acute pancreatitis.

The remaining 8 patients introduced CI at hospital discharge starting from 11 POD, with a recipient age of 49 years on average (range 29-62 years), donor age 60 years on average (range 27-80),

MELD 16 (range 10-22), D-MELD 956 (range 270-1600), follow-up days 3297 days (range 1345-4433 days). Among these, 3 patients died of lung cancer, esophageal cancer and stomach cancer.

The control group was 12 patients on full dosage CNI immunosuppression, with the same selection criteria. In this group the clinical aspects on average were: recipient age 52 years (range 30-63 years), donor age 74 years (range 38-88), MELD 14 (range 7-44), D-MELD 1026 (range 608-3256), follow-up days 1507 days (range 858-3637 days). Among these 1 patient died of hepatocellular carcinoma (HCC) de novo.

Table 1. Clinical features of LT recipients in avoiding CI protocol.

	ECP ***(n=90)***	**NO ECP** ***(n=12)***	**p**
Age (years) n±DS	48,8±10,9	51,8±11,5	<0,001
Gender M/F	65/25 (72/28)	10/2 (83/17)	0,41
MELD at LT n±DS	15,7±6,8	14,3±9,8	0,53
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HCC Y/N	24/66 (27/73)	6/6 (50/50)	0,09
Donor age n±DS	59,2±19,7	74±15,2	0,014
Patient survival 1 year (%)	98,8	100	ns
Patient survival 5 years (%)	70,8	83,3	
Mean follow up time (years) n±DS	5,7±0,7	7,9±1,0	

Analyzing the data more thoroughly, we extracted a second table (Table 1 bis) where we entered into the ECP group only patients who completed at least 6 apheresis sessions. The results that emerged need further consideration.

Table 1 bis. Clinical aspects of LT recipients in avoiding CI protocol with at least 6 ECP sessions in the ECP group.

	ECP group (n=43)	**NO ECP group (n=57)**
Recipient age in years n (range)	50,8 (28-83)	48 (16-69)
Donor age in years n (range)	57,3 (18-83)	64,1 (15-88)
MELD at LT n (range)	16 (3-35)	15 (4-44)

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AB0-incompatible protocol (AB0-I)

Currently, LT is the only clinically effective treatment option available for patients with acute and chronic liver failure. Expansion of the donor pool by improving the results of the AB0-I group is considered to be of great importance, with particular regard to patients who are rapidly deteriorating due to hepatic failure. So AB0-I LT is a therapeutic opportunity but it is a high-risk procedure, due to the potential for Antibody-Mediated Rejection (AMR) related to the presence of antiblood-type antibodies (27). AMR, as reported by the International Panel, describes humoral rejection as severe allograft dysfunction without an obvious cause, occurring in a presensitized patient immediately after or during the first week after transplantation (28).

The Liver Transplant program of the University of Pisa began in January 1996 and a total of 665 procedures were performed on 623 patients by December 31, 2005. In the same period 19 (2.8%) patients underwent AB0-I LT. Because of all the difficulties in AB0-I LT we thought of a protocol that included a novel immunomodulant AMR prophylaxis, previously described in the form of a case report (29): we introduced ECP in the prophylaxis of acute cellular rejection in AB0-I LT recipients. However, Therapeutic Plasma Exchange (TPE) and ECP associated with triple immunosuppression were not able to prevent AMR. A cornerstone in our immunomodulation therapy is the introduction, for AMR prophylaxis, of high-dose polyclonal class G immunoglobulins, which are recognized to be effective for the treatment of AMR (30, 31). A standard therapy was maintained with CI-based triple immunosuppression, achieving favorable graft survival rates, with no need for further treatment (i.e. splenectomy or hepatic drug infusion).

Adult patients who had undergone transplantation required consent as an inclusion criterion. No exclusion criteria were contemplated. After screening for compliance with the current protocol, patients were required to provide written consent for enrollment (parent or legal guardian for "UNOS status 1" patients). Pretransplantation all patients underwent single-volume TPE using fresh frozen plasma that was AB0 compatible with the donor liver to remove anti-AB0 antibodies. After LT, TPE was indicated daily only when the anti-AB0 titer would be >8. All patients of Group 2 received the first IVIg (SandoglobulinTM, ZLB Behring AG, Bern, Switzerland) administration during the anhepatic phase at a dosage of 1 g/kg and eventually for 14 POD only at the end of every TPE procedure. Therefore, during the first 14 POD TPE was not performed and IVIg was not administered if the anti-AB0 titer was <8. After POD 14, IVIg and TPE were stopped irrespective of the anti-AB0 titer based on international data (32). In regard to immunomodulatory therapy, ECP was adopted in order to reduce (or prevent) cell-mediated rejection. Treatment was initiated in the first week post-LT. The schedule was as follows: day 2, 4, and 6 post-LT; then once a week for the first month, then weekly or monthly depending upon the results of LFT. The drug protocol adopted for prophylaxis of rejection varied according to the availability of new immunosuppressive drugs over the years. At first we adopted a triple immunosuppression with steroids (S) (6-methylprednisolone) 10 mg/kg on graft reperfusion tapered in the third post-transplant month, CyA, and azathioprine (AZA). Later, we added induction with anti-CD25 monoclonal antibodies (basiliximab, SimulectTM, Novartis, Basel, Switzerland) 20 mg i.v. on post-transplant days 1 and 4. Eventually, AZA at the dose of 1 mg/kg/day was replaced by MMF at a dose of 2 g/day and withdrawn by month 6. Finally, CyA at the dose of 10 mg/Kg/day was replaced by TAC at a dose of 0.1 mg/kg/day. The efficacy of the protocol (1 g/Kg after TPE) was suitable for maintaining IgG blood levels not higher than the ones achieved in the setting of long-standing chronic diseases. A high IVIg level was selected due to previous experimental experience in the guinea-pig-to-rat model, working on the dose-effect relation in hyperacute rejection prophylaxis (33).

The study's primary endpoint was to reduce AMR and other complications related to AB0-I LT (i.e. arterial and biliary complications, acute or chronic rejection). The secondary endpoints were to evaluate the efficacy, safety, and tolerability of the treatment, in terms of graft survival, major and minor adverse effects, and in-hospital patient mortality. At the follow-up average of 568 days, TPE in combination with IVIg and ECP seems to protect the graft from AMR in AB0-I (34).

Thanks to these results, an additional 12 patients were enrolled. They have the following clinical aspects on average: recipient age 55 years (range 38-83 years), donor age 55 years (range 17-83), MELD 14 (range 11-18), D-MELD 863 (range 608-1079), and follow-up days 2836 days (range 706-4335 days).

Three patients (25%) were censored at the last follow-up (01/2017) for acute myocardial infarction, HCC-recurrence, and only one HCV-recurrence. None of the 12 patients undergoing ECP developed an acute rejection after a mean follow-up of 2836 (range: 706-4335) days.

Table 2. Donor and recipient clinical features of AB0-incompatible LT treated with ECP

Recipients (n=12)	
Age (years) mean n (range)	55 (38-63)
Gender M/F n (%)	7/5 (58/42)
MELD at LT n (range)	13 (11-18)
D-MELD n (range)	863 (608-1079)
Hospital stay (days) n (range)	27 (13-70)
1 year graft survival (%)	100
5 year graft survival (%)	75
Follow up (years) n (range)	7,8 (2,0-12)
Donors (n=12)	
Age (years) mean n (range)	55 (17-83)
Gender M/F n (%)	6/6 (50/50)

HCV protocol

End-stage liver disease caused by hepatitis C virus (HCV) represents one of the most frequent indication for LT (35). The adoption of strong immunosuppressive regimens and the increasing use of grafts from older donors are associated with a worsening trend in the prognosis of the HCV recurrence (36, 37, 38). HCV recurrence was diagnosed when an increase in HCV-RNA preceded or accompanied an increase of alanine aminotransferase (ALT).

In particular, poor survivals are more frequent with donors older than 40 years. The antiviral treatment with a combination of interferon (IFN) plus ribavirin (RBV) has limited efficacy and relevant side effects in the LT setting, therefore it is usually recommended on histologic evidence of progressive recurrent hepatitis (39). Managing IFN and RBV side effects in the context of an immunosuppressed patient early after LT is really difficult.

In 2004, when no direct antiviral drugs (DAA) were available, and the possibility of HCV recurrence was a frequent and severe post-transplant complication, we introduced ECP in association with low-standard immunosuppression (CI and anti-CD25 monoclonal antibodies, Ab-CD25) and preemptive antiviral therapy in HCV patients (40), in order to investigated the potential of the application of ECP in HCV positive recipients to decrease the burden of immunosuppression and allow an early introduction of antiviral treatment with IFN and RBV. This combined treatment was called the “HCV protocol”, which includes ECP in the prophylaxis of acute rejection of LT.

LT was performed in accordance with the international standards of informed, uncoerced consent of organ donors and prohibitions of organ trafficking. All patients provided a written informed consent for medical and surgical procedures evaluated in this study, which have been approved by the Ethical Committee of our hospital.

Based on the time of LT, three major groups of patients with similar immunosuppressive regimens for prophylaxis and treatment of the acute rejection could be identified.

In 133 patients (1996-2000) who mainly received a triple therapy with steroids, CyA, and AZA, the first-line organ rejection treatment was with steroid boluses and the second line was with OKT3.

In 91 patients (2001–2003) who mainly received a double-drug regimen with steroids and CyA and induction with Ab-CD25, the first-line organ rejection treatment was an increased dose or a switch of the CI, the second line was with steroid boluses, and the third line the use of ECP.

78 patients (2004-June 2006) mainly received a monotherapy with CyA associated with ECP and an induction with Ab-CD25. ECP was performed on days 2 and 6 post-LT, then at weeks 2, 3, 4, 6, 8, 10, and 12 and monthly thereafter for the first year post-LT. First-line rejection treatment was an increased dose or a switch of the CI with increased frequency of ECP. The second-line treatment was with steroid boluses and the third line was retransplantation.

The third group that had benefited from ECP had a lower mortality, a better survival graft, even with a graft over 70 years.

Therefore, from 2003 to 2010, 355 patients affected by end-stage liver disease secondary to HCV infection were transplanted, and 261 benefited from the ECP. The “HCV protocol” was implemented in 261 (73%) patients while 94 (27%) were treated with a standard steroid-free triple immunosuppressive regimen (CI, antimetabolites and anti IL-2) without HCV recurrence prophylaxis.

The ECP group was composed of 261 patients. The steroid-free immunosuppressive protocol consisted of induction with anti-CD25 monoclonal antibodies 20 mg i.v. on post-transplant day 1 and 4; MMF or AZA at a dosage of 2 g/day and 1 mg/kg/day, respectively. CI were introduced as clinically indicated with the goal of sparing or delaying CI introduction in order to avoid CI toxicity. ECP was performed on days 2 and 6 post-LT, then at weeks 2, 3, 4, 6, 8, 10, and 12 and monthly thereafter for the first year post-LT. First-line rejection treatment was an increased dose or a switch of the CI with increased frequency of ECP, and the third line was re-transplantation.

The clinical features on average were: recipient age 54 years (range 27-68), donor age 63 years (range 16-88), MELD 13 (range 6-33), D-MELD 790 (range 150-2336), hospital stay 23 days

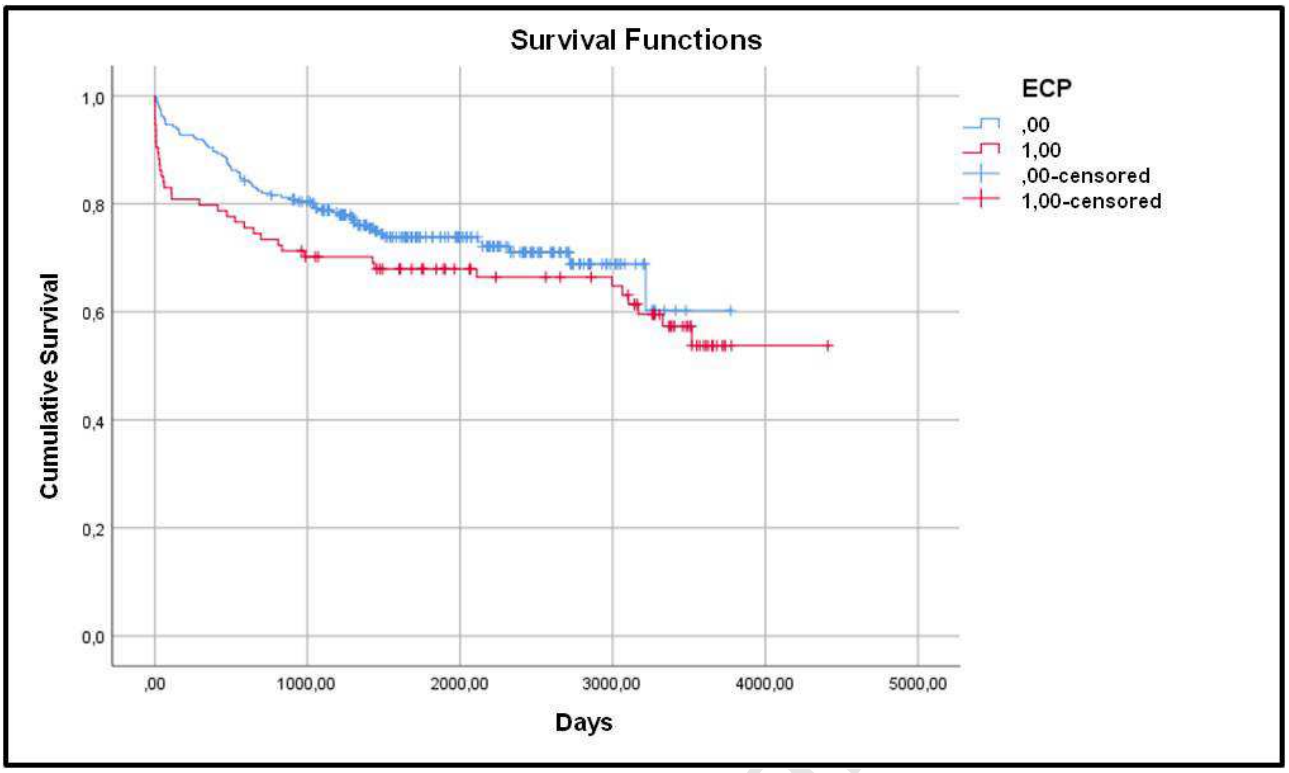
(range 7-240 days). The reason for graft loss and death in the ECP group are the following: 86 patients had HCV recurrence and 38 eventually died; only 1 patient died after organ rejection.

The control group was of 94 patients. They received the same immunosuppressive protocol without the ECP support. The clinical features on average were: recipient age 53 years (range 15-67), donor age 57 years (range 4-87), MELD 13 (range 6-33), D-MELD 688 (range 60-1944), hospital stay 21 days (range 3-100 days). The reason for graft loss and deaths in the NO ECP group are the following: 13 patients had HCV recurrence and 9 subsequently died.

Table 3. LT clinical features stratified by ECP study group.

	HCV positive recipients (n=355)				
	ECP group (n=261)		**NO ECP group (n=94)**		**p**
DONOR AGE YEARS (range/n)	16-88	63,1	4-87	56,8	0,002
RECIPIENT AGE YEARS (range/n)	27-68	53,6	15-67	52,8	0,41
MELD n	±4.4	12,6	±4.6	12,6	0,97
D-MELD n	150-2336	790	60-1944	688	0,01
LIVING AT 2017 (%)	191	73	55	58	
HOSPITAL STAY (days)	7-240	23	3-100	21	0,16
1 year graft survival (%)		90,4		79,8	
5 year graft survival (%)		73,9		67,9	
HCV RECURRENCE (n)	86	death 38	13	death 9	

Image 1. The survival trend in the ECP group (blue line) and the control group (red line).



Very interesting information emerged from data analysis regarding the survival trend in the two groups. The ECP group has a perioperative mortality lower than the control group, although the postoperative days are the most delicate.

The HCV Protocol at the moment is suspended because of the introduction of new antiviral drugs (41).

CONCLUSIONS

According to our experience we assess that ECP has the potential to be a key factor in several immunosuppressive regimens in LT, such as in AB0-incompatible LT, delayed CI introduction or in HCV positive recipients not eligible for DAA treatment in order to control HCV viremia. Our results show low complication rates both in terms of survival and quality of life. While the "HCV Protocol" is at the moment suspended due to the recent introduction of DAA, "AB0 incompatible

protocol" and "Avoiding CI protocol" are still applied, safeguarding the notion that the ECP can provide a powerful immunomodulation to be implemented in new areas to explore.

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