European multi-center study on the real-world use and clinical impact of extracorporeal photopheresis after heart transplantation

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Title page

Title **European multi-center study on the real-world use and clinical impact of extracorporeal photopheresis after heart transplantation**

Running Title **Real-world use of photopheresis after heart transplantation**

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List of non-standard abbreviations

ACR = Acute cellular rejection

AMR = Antibody-mediated rejection

CAV = Cardiac allograft vasculopathy

CMV = Cytomegalovirus

DSA = Donor-specific antibodies

EBV = Epstein-Barr virus

ECP = Extracorporeal photopheresis

GDPR = European General Data Protection Regulation

HTx = Heart transplantation

ISHLT = International Society of Heart and Lung Transplantation

SD = Standard deviation

Keywords heart transplantation, rejection, prevention, extracorporeal

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Abstract

Background: Aim of this study was to describe the real-world use of extracorporeal photopheresis (ECP) and assess its impact on clinical outcomes in the modern era of heart transplantation.

Methods: Seven transplant centers from five European countries participated in this retrospective, observational, single-arm chart review study. All patients received ECP after heart transplantation in 2015 or later. Data were extracted from medical records between November 2020 and December 2021.

Results: Overall, 105 patients were enrolled and followed for an average of two years after initiation of ECP. Reasons to start ECP were acute cellular rejection (35.2%), rejection prevention (32.4%), mixed rejection (18.1%), and antibody-mediated rejection (14.3%). Rejection ISHLT grades improved from start to end of ECP treatment in 92% of patients treated with ECP for rejection. Of patients who started ECP to prevent rejection, 88% remained free from any rejection despite a reduction of calcineurin inhibitors. Overall survival was 95%, and no deaths were related to ECP. Safety events occurred in 18 patients, of which 13 experienced complications with venous access.

Conclusions: This study, the largest European ECP study in heart transplantation, demonstrates that ECP can effectively be used to treat different rejection types and to prevent rejection in the modern era of immunosuppression. Patients with rejections who have received ECP have shown high response as measured by histological improvements in ISHLT classification. A high percentage of patients in the prevention group remained free from rejection despite reduction in immunosuppression, in particular calcineurin inhibitors.

Introduction

Survival of heart transplant recipients has improved in recent decades thanks to medical innovations.[1] However, transplant rejection and infection remain main causes of death in patients after heart transplantation (HTx).[2] In transplant rejection, the contribution to graft failure and mortality has shifted from acute cellular rejection (ACR) towards antibody-mediated rejection (AMR), which accounts for up to 40% of deaths before year 5.[3] Whereas infections either result from intense rejection treatment or general chronic overimmunosuppression due to non-individualized immunosuppressive therapy.[4]

The International Society of Heart and Lung Transplantation (ISHLT)[5] and other scientific societies[6-8] recommend extracorporeal photopheresis (ECP) as therapy for the prevention of acute rejection and as treatment of refractory ACR post-HTx. In clinical practice, ECP is also used to treat AMR, to prevent rejection in patients at high risk of transplant rejection, or to reduce immunosuppression in high-risk patients.[9-11]

ECP is a blood-based immunomodulatory therapy where leukocytes are exposed to 8-methoxypsoralen followed by ultraviolet A irradiation outside of the patient's body before re-infusion.[12] It was first approved by the U.S. FDA in 1988 for palliative treatment of cutaneous T-cell lymphoma. Additional approval for graft-versus-host disease followed as did recommendations in other disorders such as solid organ transplantation.[13] The mode of action has not been completely elucidated. Early theories focused on initiation of apoptosis in lymphoid cells. Later, theories shifted towards immunomodulatory processes involving induction of secretion of cytokines leading to a shifted immune balance.[14]

Several randomized[15-18] and non-randomized controlled[19-22] or uncontrolled[11,23-32] studies have demonstrated the effectiveness of ECP in rejection reversal and prophylaxis post-HTx.[13,33] Most of them were single-center studies with small patient numbers that were conducted prior to the introduction of tacrolimus and mycophenolate mofetil in routine clinical practice. Therefore, aim of this study was to describe the real-world use of ECP across seven European heart transplant centers and assess the effectiveness and safety of ECP in the modern era of HTx.

Material and methods

Study design and study period

Seven transplant centers located in Austria, Germany, France, Hungary, and Italy participated in this descriptive, retrospective, observational, single-arm chart review study. Data from HTx up until last visit for patients with ongoing ECP treatment and up until a maximum of 2 years after last ECP treatment for patients who completed ECP was extracted from medical records of eligible patients into electronic case report forms between November 2020 and December 2021. Prospective data were not collected.

Study population and subgroups

Patients who started ECP treatment post-HTx from 2015 onward were included. Those with a combined heart-lung transplantation were excluded as the study focused on HTx only.

Distinct subgroups of patients were investigated based on the reason for ECP treatment: ACR, AMR, or mixed rejection (ACR+AMR), and prevention of rejection. The prevention of rejection subgroup included patients who started ECP treatment without biopsy-proven rejection and with standard or reduced immunosuppressive therapy e.g., patients with skin carcinoma, recurrent CMV infections, chronic renal failure, and suspected high-grade lymphoma.

Outcomes

The study outcomes included patient characteristics, medical history, ECP treatment characteristics, concomitant treatments, graft function, response to ECP treatment, complications incl. infections, overall survival, and ECP-related safety.

As visits and examinations of patients at the transplant centers did not follow a pre-specified, uniform schedule due to the retrospective, observational study design, the timing of visits and examinations varied between participating transplant centers and included patients. This means that outcome examinations were not always available for the exact day of ECP treatment start and end. Therefore, a 2-month period was applied to assign visits and examinations to the start and end of ECP treatment.

Graft function was assessed using ejection fraction measured mainly by echocardiography. Change of graft function was defined by ejection fraction reported at start and end of ECP treatment. If ejection fraction had increased or decreased by at least 15 percentage points, graft function was classified as improved or as worsened, respectively. Otherwise, graft function was rated as stable. However, if ejection fraction measures were not available at start and end of ECP treatment, ACR and AMR ISHLT grades determined graft function change, meaning if the rejection remained stable or improved by at least one grade from start to end of ECP treatment, graft function was classified as stable.

Response to ECP treatment in the rejection subgroups was assessed by ACR and/or AMR ISHLT grades[34] reported at start and end of ECP treatment. If ACR and/or AMR had improved by at least one grade, the patient was classified as a responder. If ACR and/or AMR had worsened by at least one grade, the patient was classified as a non-responder. Patients with the same grade at the start and end of ECP treatment were classified neither as responder nor non-responder.

Response to ECP treatment in the prevention of rejection subgroup was defined by onset of biopsy-proven rejection. If no ACR, AMR, and mixed rejection developed after start of ECP treatment, the patient was classified as responder.

Statistical analysis

Descriptive statistics were applied for all outcomes. Quantitative outcomes were analyzed in terms of mean, standard deviation (SD), median, minimum, and maximum. Patient counts and percentages were calculated for qualitative outcomes.

No imputation for missing data was performed. Instead, the number of patients included in each analysis is reported.

Data protection and data quality control

Data collection and management complied with GDPR and only pseudonymized data was entered into electronic case report forms. To maximize data quality, all investigators and personnel of participating transplant centers were trained on the electronic case report forms and data collection procedure. Data was validated at point of entry by electronic checks for consistency,

completeness, and plausible value ranges that were incoporated in the documentation system and by manual remote monitoring. Any inconsistencies, missing information, and implausible values were queried to the transplant centers who were able to refer back to patient records until resolution.

Ethics and informed consent

All required ethics board approvals and patient informed consents have been obtained. All local investigators confirmed compliance with the ISHLT Statement on Transplant Ethics.

Results

Patient characteristics and medical history

Overall, 105 heart transplanted patients treated with ECP were enrolled in this study. They were followed for a mean time of 25.1 (SD 16.8) months from ECP treatment initiation to last visit at the transplant center (follow-up time for outcome overall survival). Mean time from ECP treatment initiation to last visit right-censored at 2 years after end of ECP treatment was 22.5 (SD 13.7) months (follow-up time for outcomes graft function, response, and complications). Mean age of patients at start of ECP was 47.7 (SD 14.4) years (min. 16 years to max. 74 years). Most patients (70.5%) were male.

Cardiomyopathy was the main reason for HTx (n=81 patients; 77.1%), followed by coronary heart disease (n=11 patients; 10.5%), heart valve disease (n=5 patients; 4.8%), and myocarditis (n=5 patients; 4.8%).

For details on patient characteristics and medical history see **Table 1**.

ECP treatment characteristics

Median time from HTx to first ECP treatment was 359 days (min. 20 days to max. 16 years). The main reason to start ECP treatment was ACR (n=37 patients; 35.2%), followed by prevention of rejection (n=34 patients; 32.4%), mixed rejection (n=19 patients; 18.1%), and AMR (n=15 patients; 14.3%) (**Figure 1**). All rejections were biopsy-proven except for 1 AMR. This patient presented with donor-specific antibodies (DSA) and reduced left ventricular function as well as diastolic dysfunction determined by echocardiography.[10]

At time of data extraction, 58 patients (55.2%) had completed their ECP treatment and in 47 patients (44.8%) ECP treatment was ongoing. On average, 37 (SD 32) single ECP treatments were performed over a mean duration of 13.4 (SD 12.8) months. One treatment cycle usually consisted of 2 single ECP treatments on 2 consecutive days, and mean time between treatment cycles was 18.8 (SD 20.3; median 14.0) days. The mean treatment duration for patients with ongoing ECP treatment was 18.8 (SD 15.4) months and for patients who completed ECP treatment 9.0 (SD 8.0) months. Stratified by subgroups, the mean number of single ECP treatments and the mean treatment duration was highest in patients who started ECP to treat mixed rejection or to prevent rejection (**Table 2**). However, when the number of single ECP treatments is evaluated in relation to the treatment duration in patients who had completed ECP treatment, AMR patients received on average the most single ECP treatments (3.6) per month. Overall, the treatment was more intense in the first 3 months than compared to the next two 3-month periods. For details on treatment status and schedules see **Table 2**. The **Supplement** provides details on treatment intensity.

Treatment response was the reason to stop ECP treatment according to local investigator's assessment in 56.9% (n=33 patients) of all 58 patients who completed ECP. Regular end of ECP treatment was reported for another 15.5% (n=9 patients) who were all part of the prevention of rejection subgroup. Other reasons to stop ECP treatment according to local investigator's assessment were patient preference (n=6 patients; 10.3%), unspecified complication (n=3 patients; 5.2%), difficult venous access (n=2 patients; 3.4%), non-response to ECP treatment (n=2 patients; 3.4%), death (n=2 patients; 3.4%), and non-compliance with the mask mandate during the COVID-19 pandemic (n=1 patient; 1.7%).

Concomitant treatments

All patients started ECP treatment while on immunosuppressive therapy, and all but one patient from the prevention of rejection subgroup remained on immunosuppressants until last reported visit prior to data extraction. Tacrolimus was the most frequently used immunosuppressant, followed by mycophenolate derivatives. The number of patients on steroid therapy decreased

slightly over time. Rituximab and plasma exchange/immunoadsorption were rarely chosen treatment options (**Table 3**).

For patients with ongoing ECP treatment who remained on steroid therapy (n=34 patients), 41.2% (n=14 patients) received a reduced steroid dose (-63% on average) at last reported visit prior to data extraction compared with the start of ECP treatment. The steroid dose was stable in 52.9% (n=18 patients) and increased in 5.9% (n=2 patients). For patients who completed ECP treatment who remained on steroid therapy (n=42 patients), 52.4% (n=22 patients) received a reduced dose (-67% on average), 42.9% (n=18 patients) a stable dose, and 4.8% (n=2 patients) an increased dose at last reported visit prior to data extraction – but after ECP treatment completion – compared with the start of ECP treatment.

In patients who completed ECP treatment from the prevention of rejection subgroup (n=19 patients), 16 patients (84.2%) received tacrolimus at start of ECP treatment and at last reported visit prior to data extraction. Tacrolimus trough levels were available in 11 of these patients and decreased (-34% on average) in 7 patients (63.6%). Similar results were found for the other subgroups. The dose of mycophenolate derivatives remained stable in most patients of all subgroups. For details see **Supplement**.

Graft function

Among the 58 patients who had completed ECP treatment, 36 patients had at least one of the relevant examinations (either ejection fraction [n=33 patients] or ACR/AMR ISHLT grades [n=3 patients], see methods section) at start and end of ECP treatment to assess graft function change. Mean ECP treatment duration in these patients was 7.6 (SD 6.5) months. In 35 of those 36 patients, graft function was stable at end of ECP treatment compared to ECP treatment initiation and 1 patient showed improved graft function. Mean ejection fraction was 58.4% (SD 9.1 percentage points) at start of ECP treatment and 59.3% (SD 7.3 percentage points) at end of ECP treatment which demonstrates that most patients had normal ejection fraction at start and end of ECP treatment. Similar results were found when comparing graft function at start of ECP treatment with last recorded visit prior to data extraction. See **Table 4** for details.

Response

Rejection subgroups

Of 39 patients who completed ECP treatment from the ACR, AMR, or mixed rejection subgroups, 26 patients had a biopsy at start and end of ECP treatment. Their mean ECP treatment duration was 5.4 (SD 3.7) months. Of those, 24 patients (92.3%) showed an improvement of ACR and/or AMR ISHLT grading and were classified as responders at end of ECP treatment. The grading remained stable for the other 2 patients (7.7%). Regarding ACR in the ACR and mixed rejection subgroups, 10 and 11 patients had an ISHLT grade of 2R and 1R at start of ECP treatment, respectively. At end of ECP treatment, patients had a grade of 1R (n=4 patients) or 0R (n=17 patients) (**Figure 2**). Looking at AMR in the AMR and mixed rejection subgroups, 6 and 4 patients started ECP treatment with an ISHLT grade of pAMR2 and pAMR1, respectively. At end of ECP treatment, 3 and 7 patients had a grade of pAMR1 and pAMR0, respectively (**Figure 3**).

Longer-term response was assessed for 18 patients from the ACR, AMR, or mixed rejection subgroups who had a biopsy at start and after their end of ECP treatment. On average, the 2 biopsies were performed 20.7 (SD 10.7) months from each other. Of those 18 patients, 15 (83.3%) were classified as responders and 1 patient (5.6%) as non-responder. The ACR and/or AMR ISHLT grading was stable for the remaining 2 patients.

Prevention of rejection subgroup

Of the 34 patients from the prevention of rejection subgroup, 30 (88.2%) remained free from any rejection after starting ECP treatment over a mean follow-up of 26.1 (SD 12.9) months despite being considered at high risk of rejection. Four patients developed non-hemodynamic compromised ACR while on a calcineurin inhibitor (CNI)-free regimen or after non-adherence to ECP schedule. ECP treatment was continued on a CNI regimen or after improving adherence. Another 2 patients developed DSA without biopsy-proven or clinically suspected rejection.

Complications

Overall, 17 of 105 included patients (16.2%) experienced a complication after ECP treatment initiation. Most common complications were infections (n=13 patients, 12.4%), of which 8 patients

(7.6%) had a non-CMV infection and 5 (4.8%) a CMV infection. Four patients (3.8%) experienced an endocrine/respiratory/blood/cardiac disorder, 2 patients (1.9%) an intolerance of high-dose immunosuppressive therapy, and 1 patient (1.0%) an acute kidney injury.

Overall survival

Overall survival was 95.2% among all 105 included patients over a mean follow-up of 25.1 (SD 16.8) months. Of the 5 deceased patients, 3 died with a functioning graft and 4 died after end of ECP treatment. These patients were distributed across all subgroups (n=1 patient for ACR, AMR and prevention of rejection; n=2 patients for mixed rejection). No deaths were related to ECP.

ECP-related safety

In total, 18 of 105 included patients (17.1%) had at least one ECP-related safety event, of which 13 patients (12.4%) experienced complications with venous access and 2 stopped their ECP treatment as a result. Furthermore, 6 patients (5.7%) had ECP-related anemia, 3 patients (2.9%) ECP-related hypotension, 1 patient (1.0%) ECP-related fever, and 2 patients (1.9%) an unspecified ECP-related safety event, but none of them discontinued their ECP treatment as a result.

Discussion

ECP is recommended as therapy for the prevention of acute rejection and as treatment of refractory ACR after HTx by scientific societies.[5-8] In clinical practice, ECP is also used to treat AMR, to prevent rejection in patients at high risk of transplant rejection, or to reduce immunosuppression.[9-11] Previous studies investigating the effectiveness of ECP post-HTx often included few patients from single centers or were performed prior to introduction of tacrolimus and mycophenolate mofetil in routine clinical practice. The results of this study with more than 100 patients demonstrate that ECP was most frequently used to treat ACR and to prevent rejection e.g., in patients with malignancies, recurrent infections or chronic renal failure, but also to treat AMR and mixed rejection. Treatment schedules varied depending on the reason for ECP treatment. The average treatment duration was highest for the management of mixed rejection and in rejection prevention. On average, a pattern of ECP on 2 consecutive days every 2 to 3 weeks was applied by heart transplant centers for all indications.

Graft function was stable for almost all patients throughout the study and response to ECP treatment was significant. In patients who started ECP to treat ACR, AMR or mixed rejection, 92% showed an improvement of ACR and/or AMR ISHLT grading after a mean ECP treatment duration of 5.4 months. The remaining patients had stable ISHLT grades. Rejection reversal with ECP was also shown by Costanzo-Nordin[15,16,23] and Dall'Amico[26,29]. In patients who started ECP to prevent rejection, 88% remained free from any rejection over a mean follow-up of 26 months despite patients considered at high risk of rejection and reduced immunosuppressive therapy in patients who completed ECP. Previous research on ECP for rejection prophylaxis[17,19,20] also found that ECP reduced acute rejection episodes compared to a control group without ECP. However, in these earlier studies ECP was an adjunctive tool of a standard immunosuppressive CNI regimen. Whereas in our study CNI exposure could be reduced due to ECP treatment without losing efficacy.

In our study fewer patients (19%) were hemodynamically compromised at start of ECP treatment compared to 33% in an earlier study of Kirklin et al.[21], which may reflect the difference in standard of care mainly due to the increasing effectiveness of immunosuppressive therapy[35].

Only a few patients developed an infection. Overall survival was high with 95% among all 105 patients included in this study over a mean follow-up of 25 months.

This study confirms results from earlier studies that ECP is a safe and well-tolerated treatment.[11-13,32] No major safety events occurred. Venous access complication was the most common safety event. No patient discontinued ECP treatment due to adverse events.

The study has some limitations. Effectiveness of ECP in comparison with other treatment options was not assessed due to the descriptive, single-arm design of this study.

Data generation for this observational study was not as standardized as e.g., in conventional randomized controlled trials, but subject to center-specific differences. Patient examination schedules varied and not all data were available at all centers. No source data verification was performed and therefore, transmission errors cannot be excluded. However, extracted data was validated by electronic checks for consistency, completeness, and plausible value ranges and by

manual monitoring to support data quality. Still, difficulties remained in collecting consistent DSA data as involved laboratories applied different assays and thresholds.

Reasons for chosen ECP treatment schedules were not collected for this study, but the observed schedules reflect the real-world treatment.

Not all demonstrated benefits may be solely attributable to ECP treatment as transplanted patients may have received multiple therapies at time of ECP treatment. In patients with AMR or mixed rejection, ECP is commonly used in combination with other treatments[9,10,36].

Overall, this is the largest European and first multicenter study investigating real-world use, effectiveness and safety of ECP in the modern era of HTx. In conclusion, the study results demonstrate that ECP is used to treat different types of rejection and in prevention of rejection with varied treatment schedules. This study also indicates that ECP was an effective and safe treatment in our large cohort of patients. Patients with rejection who have received ECP showed a high response rate as measured by histological improvements in ISHLT classification. Furthermore, a high percentage of patients in the prevention of rejection subgroup remained free from rejection despite reduction in immunosuppressive therapy, especially CNIs.

Financial conflict of interest statement

Dr. Markus J. Barten and Dr. Eric Epailly received honoraria and travel support form Mallinckrodt Pharmaceuticals. Dr. Balazs Sax and Dr. Johannes Gökler received speaker fees from Mallinckrodt Pharmaceuticals. Prof. Dr. Andreas Zuckermann is part of the ECP Speakers Bureau of Mallinckrodt Pharmaceuticals. Julia Theil and Kathrin Borchert are employees of Xcenda GmbH (Hannover, Germany), a company which received funding from Therakos UK (Ltd), a Mallinckrodt Pharmaceutical company, to conduct the study described herein. Andy Ingram is an employee of Mallinckrodt Pharmaceuticals. Dr. Simon Schopka, Dr. Cristiano Amarelli, Dr. Teszák, and Dr. Benedetta Natali have no conflicts of interest to declare.

Author contributions

Dr. Markus J. Barten, Dr. Eric Epailly, Andy Ingram, Julia Theil, and Kathrin Borchert contributed to the concept or design of the work. All authors contributed to the acquisition or analysis of data, data interpretation, manuscript development and final approval of the article.

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Tables

Table 1: Patient characteristics and medical history

		All	Ongoing ECP	Completed ECP
All patients	N (%)	105 (100%)	47 (100%)	58 (100%)
Gender				
Men	n (%)	74 (70.5%)	35 (74.5%)	39 (67.2%)
Women	n (%)	31 (29.5%)	12 (25.5%)	19 (32.8%)
Age at start of ECP in years				
	mean (SD)	47.7 (14.4)	44.9 (17.1)	49.9 (11.4)
	min, median, max	16, 51, 74	16, 48, 71	27, 51.5, 74
Reason for HTx				
Cardiomyopathy	n (%)	81 (77.1%)	33 (70.2%)	48 (82.8%)
Coronary heart disease	n (%)	11 (10.5%)	4 (8.5%)	7 (12.1%)
Heart valve disease	n (%)	5 (4.8%)	3 (6.4%)	2 (3.4%)
Myocarditis	n (%)	5 (4.8%)	5 (10.6%)	0 (0%)
Congenital heart defect	n (%)	1 (1.0%)	1 (2.1%)	0 (0%)
Non-compaction myocardium	n (%)	1 (1.0%)	1 (2.1%)	0 (0%)
Left ventricular outflow tract obstruction by thrombus	n (%)	1 (1.0%)	0 (0%)	1 (1.7%)
Patients with malignancy after HTx	n (%)	16 (15.2%)	6 (12.8%)	10 (17.2%)
Squamous cell skin carcinoma	n (%)	4 (3.8%)	2 (4.3%)	2 (3.4%)
Basal cell skin carcinoma	n (%)	3 (2.9%)	0 (0%)	3 (5.2%)
Bladder cancer	n (%)	1 (1.0%)	0 (0%)	1 (1.7%)
Kidney carcinoma	n (%)	1 (1.0%)	1 (2.1%)	0 (0%)
Lymphangiosis carcinomatosa	n (%)	1 (1.0%)	0 (0%)	1 (1.7%)
Morbus Hodgkin	n (%)	1 (1.0%)	0 (0%)	1 (1.7%)
Pheochromocytoma	n (%)	1 (1.0%)	1 (2.1%)	0 (0%)
Prostate cancer	n (%)	1 (1.0%)	0 (0%)	1 (1.7%)
High grade B-cell lymphoma	n (%)	1 (1.0%)	1 (2.1%)	0 (0%)
Invasive ductal carcinoma	n (%)	1 (1.0%)	1 (2.1%)	0 (0%)

Non-small cell lung cancer	n (%)	1 (1.0%)	0 (0%)	1 (1.7%)
Time from HTx to malignancy in years				
	mean (SD)	5.1 (3.8)	6.5 (5.0)	4.2 (2.6)
	min, median, max	0, 4, 13	0, 8, 13	1, 3, 9
Infections between HTx and first ECP treatment				
CMV	n (%)	27 (25.7%)	11 (23.4%)	16 (27.6%)
EBV	n (%)	6 (5.7%)	5 (10.6%)	1 (1.7%)
Comorbidities at time of HTx				
Renal insufficiency	n (%)	32 (30.5%)	15 (31.9%)	17 (29.3%)
Arterial hypertension	n (%)	24 (22.9%)	11 (23.4%)	13 (22.4%)
Hyperlipidemia	n (%)	23 (21.9%)	8 (17.0%)	15 (25.9%)
Diabetes mellitus	n (%)	15 (14.3%)	4 (8.5%)	11 (19.0%)

Table 2: ECP treatment status and schedules

	Number of patients (%)			Mean number of ECP treatments (SD) over a mean treatment duration (SD)		
	Overall	**Ongoing ECP**	**Completed ECP**	**Overall**	**Ongoing ECP**	**Completed ECP**
All patients	105 (100%)	47 (44.8%)	58 (55.2%)	37.1 (32.1) treatments over 13.4 (12.8) months	50.9 (40.8) treatments over 18.8 (15.4) months	25.9 (16.0) treatments over 9.0 (8.0) months
ACR subgroup	37 (100%)	16 (43.2%)	21 (56.8%)	32.3 (33.0) treatments over 12.0 (13.8) months	46.3 (44.9) treatments over 18.6 (18.0) months	21.7 (13.3) treatments over 7.0 (6.0) months
AMR subgroup	15 (100%)	7 (46.7%)	8 (53.3%)	26.7 (20.7) treatments over 10.0 (9.6) months	34.0 (22.4) treatments over 15.1 (10.6) months	20.4 (18.0) treatments over 5.6 (6.1) months
Mixed rejection subgroup	19 (100%)	9 (47.4%)	10 (52.6%)	43.6 (37.6) treatments over 16.5 (15.6) months	63.7 (43.6) treatments over 24.0 (16.3) months	25.6 (19.6) treatments over 9.8 (11.9) months

Prevention of rejection subgroup	34 (100%)	15 (44.1%)	19 (55.9%)	43.1 (31.3) treatments over 14,7 (11.1) months	55.9 (41.4) treatments over 17.6 (14.3) months	33.0 (14.6) treatments over 12.3 (7.3) months

Table 3: Concomitant treatments

	At start of ECP treatment n (%)	At end of ECP treatment n (%)	At last reported visit prior to data extraction* n (%)
Patients with ongoing ECP treatment (n=47)			
Immunosuppressants	47 (100%)	--	47 (100%)
Tacrolimus	33 (70.2%)	--	34 (72.3%)
Cyclosporine	9 (19.1%)	--	9 (19.1%)
Mycophenolate derivatives	35 (74.5%)	--	29 (61.7%)
Everolimus	18 (38.3%)	--	19 (40.4%)
Sirolimus	0 (0%)	--	0 (0%)
Rituximab	2 (4.3%)	--	0 (0%)
Steroids	41 (87.2%)	--	37 (78.7%)
Plasma exchange/Immunoadsorption	0 (0%)	--	0 (0%)
Patients with completed ECP treatment (n=58)			
Immunosuppressants	58 (100%)	57 (98.3%)	57 (98.3%)
Tacrolimus	47 (81.0%)	48 (82.8%)	49 (84.5%)
Cyclosporine	7 (12.1%)	6 (10.3%)	5 (8.6%)
Mycophenolate derivatives	39 (67.2%)	38 (65.5%)	40 (69.0%)
Everolimus	24 (41.4%)	24 (41.4%)	28 (48.3%)
Sirolimus	0 (0%)	0 (0%)	0 (0%)
Rituximab	1 (1.7%)	1 (1.7%)	0 (0%)
Steroids	55 (94.8%)	54 (93.1%)	47 (81.0%)
Plasma exchange/Immunoadsorption	3 (5.2%)	1 (1.7%)	0 (0%)

*After the end of ECP treatment for patients with completed ECP treatment

Table 4: Graft function change

	Overall	Patients with available examinations* at both timepoints	Patients with stable graft function	Patients with improved graft function	Patients with worsened graft function
	n	n	n (%)	n (%)	n (%)
Start versus end of ECP treatment					
Patients with completed ECP treatment	58	36	35 (97.2)	1 (2.8%)	0 (0%)
Start of ECP treatment versus last reported visit prior to data extraction**					
Patients with completed ECP treatment	58	43	42 (97.7%)	1 (2.3%)	0 (0%)
Patients with ongoing ECP treatment	47	31	29 (93.5%)	1 (3.2%)	1 (3.2%)

*Either ejection fraction or ACR/AMR ISHLT grades

**After the end of ECP treatment for patients with completed ECP treatment

Figures

Figure 1: Reasons to start ECP treatment

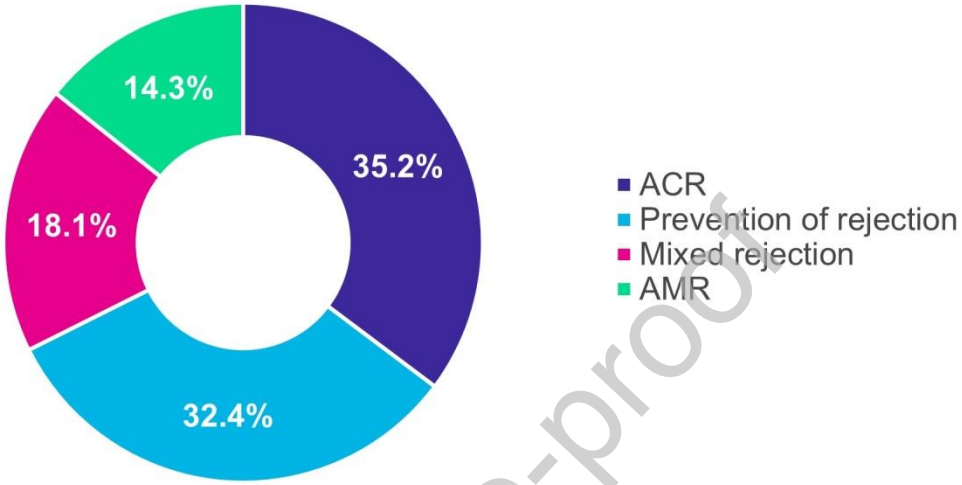

Figure 2: Sankey plot displaying the ACR ISHLT grade development from start to end of ECP treatment in the ACR and mixed rejection subgroups

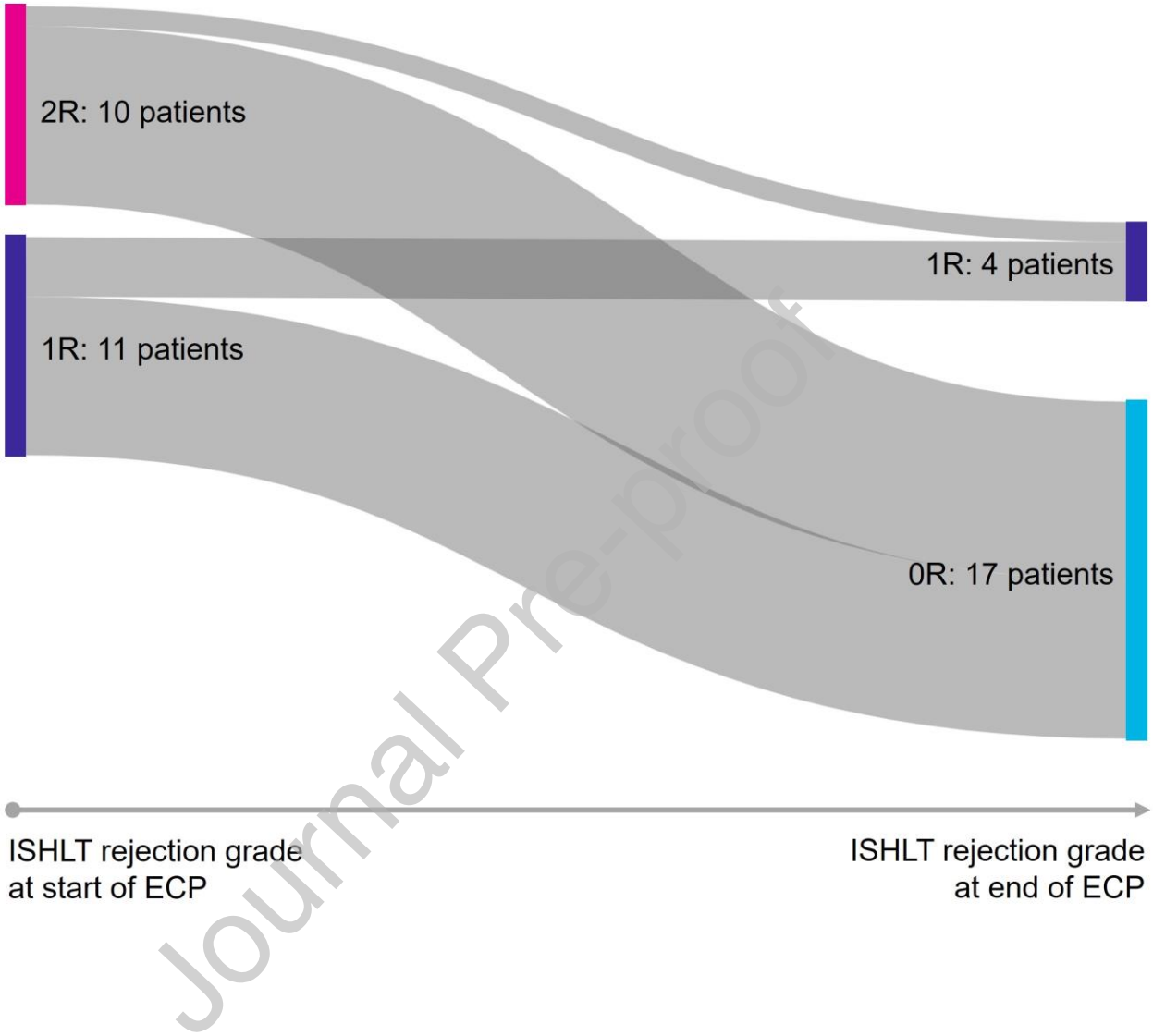

Figure 3: Sankey plot displaying the AMR ISHLT grade development from start to end of ECP treatment in the AMR and mixed rejection subgroups