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► **To cite this version:**

Mathilde Tamain, Johnny Sayegh, Arnaud Lionet, Philippe Grimbert, Carole Philipponnet, et al.. Extracorporeal photopheresis for the treatment of graft rejection in 33 adult kidney transplant recipients. *Transfusion and Apheresis Science*, 2019, 58, pp.515 - 524. 10.1016/j.transci.2019.06.031 . hal-03488035

HAL Id: hal-03488035

<https://hal.science/hal-03488035v1>

Submitted on 20 Jul 2022

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Extracorporeal photopheresis for the treatment of graft rejection in 33 adult kidney transplant recipients

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Autorship

Mathilde Tamain ^{1,2}, contributed to the research design, to the analysis of the research data and to the drafting of the present paper.

Johnny Sayegh ³, contributed to the research work and to the drafting of the present paper.

Arnaud Lionet ⁴, contributed to the research work.

Philippe Lang ⁵, contributed to the research work.

Carole Philipponnet ¹, contributed to the research work.

Marc Hazzan ⁴, contributed to the research work.

Jean-François Augusto ³, contributed to the research work.

Mathias Büchler ⁶, contributed to the research work.

Etienne Merlin ⁷, contributed to the research work.

George Kosmadakis ⁸, contributed to the drafting of the present paper.

Aurélien Tiple ¹, contributed to the research work.

Bruno Pereira ⁹, contributed to the use of new reagents and analytic tools and to the data analysis.

Cyril Garrouste ¹, contributed to the research design, to the analysis of the research data and to the drafting of the present paper.

Anne-Elisabeth Heng ^{1,2}, contributed to the research design, to the analysis of the research data and to the drafting of the present paper.

The authors declare no conflicts of interest.

Abbreviations

8-MOP, methoxypsoralen^{[1][1]}_[SEP]

AAMR, acute antibody-mediated rejection^{[1][1]}_[SEP]

ACR, acute cellular rejection^{[1][1]}_[SEP]

AMR, antibody-mediated rejection^{[1][1]}_[SEP]

Anti-HLA Abs, anti-human leukocyte antigen antibodies

ASFA, American Society for Apheresis^{[1][1]}_[SEP]

ATG, anti-thymocyte globulin^{[1][1]}_[SEP]

CAMR, chronic antibody-mediated rejection^{[1][1]}_[SEP]

CNIs, calcineurin inhibitors^{[1][1]}_[SEP]

CMV, cytomegalovirus

CTCL, cutaneous T cell lymphoma

DSAs, donor-specific antibodies^{[1][1]}_[SEP]

EBV, Epstein-Barr virus^{[1][1]}_[SEP]

ECP, extracorporeal photopheresis^{[1][1]}_[SEP]

ESKD, end-stage kidney disease^{[1][1]}_[SEP]

FMDA, factorial mixed data analysis

GFR, glomerular filtration rate^{[1][1]}_[SEP]

HAS, Haute Autorité de Santé^{[L][SEP]}

IL1 β , interleukin-1 β ^{[L][SEP]}

KT, kidney transplantation^{[L][SEP]}

MFI, mean-fluorescence intensity^{[L][SEP]}

MMF, mycophenolate mofetil^{[L][SEP]}

MP, methylprednisolone pulses^{[L][SEP]}

NK, natural killer lymphocyte^{[L][SEP]}

PBMCs, peripheral blood mononuclear cells

Abstract

Background - Extracorporeal photopheresis (ECP) has shown encouraging results in the prevention of allograft rejection in heart transplantation. However, the role of ECP in kidney transplant (KT) rejection needs to be determined.

Methods - This multicentre retrospective study included 33 KT recipients who were treated with ECP for allograft rejection (23 acute antibody-mediated rejections (AMRs), 2 chronic AMRs and 8 acute cellular rejections (ACRs)). The ECP indications were KT rejection in patients who were resistant to standard therapies (n=18) or in patients for whom standard therapies were contraindicated because of concomitant infections or cancers (n=15).

Results - At 12 months (M12) post-ECP, 11 patients (33%) had a stabilization of kidney function with a graft survival rate of 61%. The Banff AMR score (g+ptc+v) was a risk factor for graft loss at M12 (HR 1.44 [1.01-2.05], p<0.05). The factorial mixed data analysis identified 2 clusters. Patients with a functional graft at M12 tended to have cellular and/or chronic rejections. Patients with graft loss at M12 tended to have acute rejections and/or AMR; higher serum creatinine levels; DSA levels and histologic scores of AMR; and a longer delay between the rejection and ECP start than those of patients with functional grafts.

Conclusions - ECP may be helpful to control ACR or moderate AMR in KT recipients presenting concomitant opportunistic infections or malignancies when it is initiated early.

Introduction

Allograft rejection is a major issue in kidney transplantation (KT): episodes of acute allograft rejection were reported to be responsible for 12% of graft loss, with the highest risk in the first six months after transplantation.¹ Notably, antibody-mediated rejection (AMR) seems to be the leading cause of late graft failure.^{2,3}

The current immunosuppressive therapies that are used for acute allograft rejection (intravenous steroids, plasmapheresis, rituximab, and intravenous immunoglobulins) are not always effective.^{4,5} Moreover, these therapies have significant side effects, including direct toxicity and the risk of opportunistic infections and malignancies.^{6,7} In these situations, alternative methods are needed to optimize the graft outcome while minimizing the associated side effects.⁸

Extracorporeal photopheresis (ECP) is an apheresis immunomodulatory treatment consisting of three stages: (1) the collection of peripheral blood mononuclear cells (PBMCs); (2) the irradiation of PBMCs with ultraviolet A in the presence of psoralen, a photosensitizing agent; and (3) the reinfusion of treated cells to the patient.⁹ The mechanisms of action of ECP have not been completely elucidated. Ultraviolet A irradiation in the presence of psoralen provokes the cross-linking of deoxyribonucleic acid (DNA), triggering an apoptotic cascade in lymphocytes, especially activated lymphocytes. The proportion of apoptotic lymphocytes is insufficient to explain the ECP effects, but several studies have shown that the early injection of apoptotic cells induces tolerance.^{10,11} Indeed, the phagocytosis of apoptotic cells by antigen-presenting cells is responsible for a shift from a Th1 to a Th2 immune response; an increase in anti-inflammatory cytokine release (Interleukin-10 and TGF- β); a decrease in pro-inflammatory cytokine release (Interleukin-1 α , Interleukin-1 β , Interleukin-6 and TNF- α); a maintenance of the immature profile of dendritic cells; and the proliferation of regulatory cells.¹²

ECP was developed by Edelson et al. in the 1980s and was first used for the treatment of cutaneous T cell lymphoma (CTCL).¹³ The American Society for Apheresis (ASFA) guidelines list ECP as a first-line therapy for CTCL and as a second-line therapy for cutaneous forms of graft-versus host-disease and for the prevention or treatment of rejection in heart and lungs transplant recipients.¹⁴ Indeed, two prospective studies have shown that ECP combined with standard immunosuppressive therapies as a prophylactic treatment may reduce the rejection rates and severity in heart transplantation.^{15,16} In KT, several studies have been published on the use of ECP for the prevention or treatment of rejection.^{17,18,19,20,21,22,23,24,25,26,27} However, data from larger studies or prospective studies are limited or absent.

In the present study, we report the outcomes of 33 adult KT recipients with allograft rejection who were treated with ECP at 4 French Transplantation Centres. The aim of this study was to describe ECP (1) indications, (2) procedures and (3) results in kidney allograft rejection and to identify the factors influencing ECP efficacy.

Materials and methods

Study design and patients

We performed a multicentre retrospective study of 33 adult KT recipients with allograft rejection who were treated with ECP between 2001 and 2015 at 4 KT Centres: Angers (2 patients), Créteil (11 patients), Clermont-Ferrand (15 patients) and Lille (5 patients). We obtained the authorization of the local Ethics Committee (Comité de Protection des Personnes Sud-Est VI).

Data collection

Patient medical charts and demographic data were retrieved from the hospital registries. The following data were recorded: the age, gender, date of transplantation, postoperative immunosuppressive regimen, complications including cancers and infections, date of rejection, type of rejection with histologic data, rejection treatment and ECP-related data (date, indications, course and complications). We examined the KT outcomes of these patients, including the patient and graft survival, causes of graft loss, and patient death.

Rejection episodes were classified according to the Banff 2013 Classification.²⁸ An acute antibody-mediated rejection (AAMR) diagnosis required (1) histologic lesions of acute or chronic tissue injury; (2) evidence of current/recent antibody interaction with the vascular endothelium (linear C4d staining in peritubular capillaries or at least moderate microvascular inflammation: $g+ptc \geq 2$); and (3) the presence of circulating DSAs. A chronic antibody-mediated rejection (CAMR) diagnosis required (1) histologic lesions of chronic tissue injury; (2) evidence of current/recent antibody interaction with the vascular endothelium; and (3) the presence of circulating DSAs.²⁸ We extended these definitions to patients with at least 2 of the criteria. The composite scores of the Banff classification were used; acute composite score consisted of the sum of tubulitis (t), intimal arteritis (v), inflammation (i), glomerulitis (g), and peritubular capillaritis (ptc), whereas the chronic composite score included the sum of the

chronic changes in the interstitium (ci), tubules (ct), glomerulus (cg), and vessels (cv). The acute microvascular-inflammatory score consisted of the sum of g and ptc. The acute composite AMR score consisted of the sum of g, ptc, and v. The acute composite ACR consisted of i, t, and v.²⁹

The stabilization of kidney function was defined as the absence or less than a 10% increase in the serum creatinine levels, whereas the worsening of kidney function was defined as the increase of serum creatinine levels of more than 10% of the baseline values.

Donor-Specific Antibodies (DSAs)

DSAs are expressed as the mean-fluorescence intensity (MFI). If the anti-human leukocyte antigen (anti-HLA) data were missing, old serum samples were used, if available, to perform a local identification of DSAs using a LABScreen® Single Antigen kit (One Lambda®). DSA specificity was defined as an MFI > 1000. A decrease in the DSA MFI > 25% was considered meaningful.³⁰

ECP procedure

During the procedure, patient blood was collected from a peripheral (n=4) or central venous access (n=4) or from an arteriovenous fistula (AVF) (n=25). The peripheral blood mononuclear cells (PBMCs) were separated by cytapheeresis in parallel with the reinfusion of the processed blood to the patient. Then, the PBMCs were treated with methoxypsoralen (8-MOP®). The 8-MOP could be ingested 2 h before the procedure or a liquid form of 8-MOP could be added to the cytapheeresis wells. After that, the PBMCs were exposed to ultraviolet A light with a 352 nm wavelength. Finally, the irradiated cells were reinfused into the patient.

Two kinds of techniques were available. The first one was an open system using two unconnected instruments: a flow-cell separator (Spectra Optia®, Cobe Spectra®, COM.

TEC®, Amicus® or Haemonetics MCS Plus®) and another device for cell irradiation (PIT System®, Theraflex-ECP® or Macogenic®). The second was a closed system in which the separation, irradiation and reinfusion of the cells were fully integrated and performed automatically (Therakos® UVAR XTS and CELLEX® Photopheresis System).³¹ A treatment session was defined as one ECP procedure.

Statistical Analysis

Statistical analysis was performed using Stata software (StataCorp, College Station, US). All tests were two-sided, with a type I error of 0.05. Continuous data are expressed as the mean \pm standard deviation or as the median [interquartile range], according to the statistical distribution (the assumption of normality was assessed using a Shapiro-Wilk test). Continuous parameters were compared between independent groups using a Student's t-test or Mann-Whitney test if the assumptions of the t-test were not met ((1) normality and (2) homoscedasticity, as studied with a Fisher-Snedecor test). Concerning categorical parameters, the comparisons were performed using a chi-squared test or, when appropriate, Fisher's exact test. Due to the sample size, non-parametrical tests have often been preferred. Censored data were estimated by the Kaplan-Meier method (the Ying and Wei estimation of variance was used to take the centre effect into account) and were compared between groups by a marginal proportional hazards Cox model to consider the between- and within-centre variability.

These analyses were completed with multidimensional factorial analysis (factorial mixed data analysis, such as FMDA, to analyse the assets as the elements of qualitative and quantitative variables) to uncover the underlying relationships and structures (latent constructs) and to aggregate the subjects into clusters such that each cluster represented a topic to better describe the factors associated with the ECP results.³² The parameters that were selected to be included in the FMDA were determined based on the univariate results and clinical relevance. The

analytical study of the equations that were involved showed that the discriminant factors minimized the Mahalanobis distance of each group and maximized the distance between groups, providing compact groups that were spread as much as possible in the space. The usual methodology involves the transformation of the quantitative variables to categorical parameters, categorizing them into classes to ultimately use these new variables and the other variables for an exploratory multiple correspondence analysis (MCA). This methodology is relatively easy to implement and can be used when the sample size is sufficient ($n > 100$). Otherwise, the MCA could give unstable and nonrobust results. Additionally, it is interesting to retain, through methods such as FMDA, the quantitative variables, particularly in 2 situations: when the number of categorical variables is very small compared with the number of the quantitative variables and when the sample size is low.

Results

Patient characteristics (Tables 1 and 2)

The patient characteristics are summarized in Table 1. The ECP indications, courses and results are summarized in Table 2. All 33 patients had a diagnosed allograft rejection episode in a median time of 11 months [1-216] after transplantation. According to the Banff 2013 classification, the rejection episodes were AAMRs for 23 patients (70%), chronic antibody-mediated rejections (CAMRs) for 2 patients (6%), and acute cellular rejections (ACRs) for 8 patients (24%).

The ECP indications were kidney allograft rejections that were resistant to standard therapies ($n=18$); or kidney allograft rejections for patients for whom standard therapies were contraindicated due to the presence of active infections or cancers ($n=15$). Six patients (18%) had concomitant malignancy complications: 3 patients had cutaneous neoplasia (1 basocellular carcinoma, 1 cutaneous T-cell lymphoma and 1 Kaposi sarcoma), 2 patients had

B-cell lymphoma and 1 patient had combined prostatic/lung tumours. Twenty-two patients (67%) had concomitant infectious complications, including one or more episodes of the following infections: 11 bacterial infections (4 septicaemia, 3 pneumonia, 2 pyelonephritis, 1 peritonitis and 1 hepatic abscess); 17 viral infections (13 *Cytomegalovirus* (CMV), 6 *BK virus*, 2 *Epstein-Barr virus* (EBV)) and 1 *Pneumocystis jiroveci* pneumonia.

Five patients (15%) received no additional treatment other than ECP. The other 28 patients received the associated treatments that are described in Table 2.

ECP procedure

ECP sessions were performed between March 2001 and May 2015, 18 months [2-221] after transplantation and 3 months [0.5-25] after the diagnosis of a rejection episode.

The COBE® Spectra Apheresis System was used for 24 patients (73%), the THERAKOS® UVAR XTS® or CELLEX® Photopheresis System was used for 8 patients (24%), and both systems were consecutively used for 1 patient. The vascular access was an arterio-venous fistula in 25 patients (76%), tunnelled catheters in 4 patients (12%) and a peripheral venous catheter in 4 patients (12%).

ECP was initiated at a frequency of 2 sessions per week in 27 patients (82%) and one session per week in 6 patients (18%) for a period of one month. Thereafter, the session frequency was reduced during the maintenance period of the ECP treatment as follows: one session weekly, then one session every 2 weeks and finally one session monthly. Of the 6 patients who began ECP with one session a week, 5 belonged to the same centre. Patients underwent a median of 12.5 [3-60] ECP sessions over 3.5 months [0.5-67.5]. Twelve patients received less than 10 ECP procedures: 6 of these were dialysis-dependent in the month following the initiation of ECP, and 2 in the 3 months following the initiation of ECP; only one of these had a functional kidney at M12.

The reported side effects were bacterial infections in 3 patients (1 catheter-related infection, 1 case of pneumonia, and 1 case of pyelonephritis), one episode of the dysfunction of the extracorporeal circuit with blood loss requiring no transfusion in 2 patients, isolated fever during an ECP session in 1 patient and venous-access dysfunction in 1 patient. Twenty-six patients (79%) presented no side effects.

ECP results (Tables 2 and 3)

Graft survival at 12 months after ECP initiation (M12) (Tables 2 and 3; Figure 1)

Twenty patients (61%) had a functional graft at M12. Patients with a functional graft at M12 underwent a significantly longer duration of ECP (4.5 months [1-67] versus 1.5 months [0.5-11] ($p=0.05$)) and a higher number of ECP sessions (15 [7-60] versus 9 [3-29] ($p=0.04$)) compared to those of patients with a graft loss at M12. The acute composite AMR score was a risk factor for graft loss at M12 (HR: 1.44 [1.01-2.05]; $p=0.04$) (Table 3; Figure 1B).

Serum creatinine levels of more than 276 $\mu\text{mol/L}$ at ECP initiation were associated with an increased probability of graft loss at M12, with an estimated sensitivity of 80% and an estimated specificity of 75%. Serum creatinine levels of more than 412 $\mu\text{mol/L}$ at ECP initiation were associated with an increased probability of graft loss at M12, with an estimated sensitivity of 50% and an estimated specificity of 100%. The associated ROC curve is presented in Figure 2, with an area under the ROC curve of 0.82. None of the 3 patients who began ECP while they were dialysis-dependent recovered their renal function. Eight patients (24%) had a serum creatinine level higher than 412 $\mu\text{mol/L}$ at ECP initiation. Among the 13 patients with graft loss at M12, 6 were dialysis-dependent in the month following ECP

initiation and received less than 10 ECP procedures. Moreover, 4 patients were dialysis-dependent in the month following ECP completion.

Effects on the renal function at 12 months after ECP (M12) (Tables 2 and 3; Figure 1B)

Eleven patients (33%) had a stabilization of kidney function at M12. These patients had a significantly lower Banff score of the acute microvascular inflammation (0 [0-3] versus 3.5 [0-6] ($p = 0.018$)) and a significantly lower Banff acute composite AMR score (2 [0-3] versus 4 [0-6] ($p=0.018$)) compared to those of patients who did not experience a stabilization of kidney function (Table 2; Figure 1A).

Results of the Factorial Mixed Data Analysis (Figure 3)

The FMDA defined two clusters of patients. The cluster of patients with a functional graft at 12 months after ECP initiation tended to have cellular and/or chronic rejections and associated cancers. The cluster of patients with graft loss at 12 months after ECP tended to have acute and/or antibody-mediated rejections, higher serum creatinine levels, higher DSA levels, higher histologic scores of AMR and a longer delay between the rejection and ECP initiation compared to those in patients who did not experience graft loss.

Impact of ECP on the DSA MFI levels

There was no significant decrease in the immunodominant DSA MFI levels after ECP compared to those at baseline, but the pre- and post-ECP data were available for only 11 patients. Four patients presented a decrease of more than 25% of their immunodominant DSA MFI levels after ECP (14099 to 10715; 14117 to 9442; 7761 to 0 and 4000 to 1000, respectively).

Focus on ECP results in patients treated by ECP as a single therapy

Five patients (15%) were treated by ECP as a single therapy. Three of these patients had AAMR associated with either simultaneous lung and prostatic cancers, basocellular carcinoma or CMV infection. These patients all had a functional graft at M12. The total graft survival after ECP initiation was 24 and 72 months, respectively, in two patients. The other patient still had a functional graft at M24. All 3 of these patients had more than a 25% decrease in their immunodominant DSA MFI levels after ECP. One patient who was treated with ECP as a single therapy had CAMR associated with a CTCL and died with a functional graft at M22. The last patient had ACR associated with severe bacterial infections and began ECP while being dialysis-dependent and did not recover their kidney function.

Discussion

This multicentre retrospective study is the largest to report the use of ECP for kidney allograft rejection. Of the 33 patients with allograft rejections who were treated by ECP, 61% had a functional graft at M12, and 33% had a stabilization of kidney function. Interestingly, 3 patients with AAMR who were treated by ECP as a single treatment due to concomitant infections or cancers still had a functional graft at M12. Data from the literature about the use of ECP in KT are scarce and are conflicting regarding the treatment of rejection (Table 4). A case series reported 3 KT recipients with rejection episodes (2 chronic and 1 acute) who were unsuccessfully treated with ECP, which was performed on 2 consecutive days per month for 3 months.²⁰ Studies with more intensive ECP regimens seemed to report better results. Of 28 cases of KT rejections, ECP seemed to help to stabilize renal function in 14 patients (50%) and to improve renal function in 8 patients (29%).^{17,18,19,20,21,22,23,24,25,26,27} The « French Haute

Autorité de Santé (HAS) » recommended the use of ECP in the prevention of rejection in cardiac transplantation.³³ However, the evidence level was too weak to extend the recommendations to other solid organ transplantations.³³ Nonetheless, the experts reported that ECP could be used in the prevention and/or treatment of refractory acute rejection, and in cases in which immunosuppressive treatment reduction was required because of infections or post-transplantation lymphoproliferative disorders, as in most of the cases in our study.³³ A large proportion of the patients in our study (82%) had a frequency of ECP sessions that were in accordance with the standard protocol used in France (2 sessions per week for 4 weeks, followed by 1 session per week for at least 3 to 6 months).³³

This study is the first to identify predictive factors for response to ECP treatment. The FMDA highlighted that ECP could be particularly interesting in the treatment of cellular and/or chronic rejections and in the case of concomitant cancers. However, ECP had efficacy limitations. Indeed, ECP was systematically ineffective in patients with poor renal function at initiation (serum creatinine level > 412 $\mu\text{mol/L}$), which is consistent with the data in the literature.³⁴ Moreover, both univariate analysis and FMDA showed that ECP seemed to be less effective in patients with severe AAMR (high DSA levels and high histologic scores of AAMR) and in patients for whom there was a long delay between the rejection and ECP initiation. These results are consistent with the data in the literature about the efficacy of other treatments, such rituximab, plasmapheresis and intravenous immunoglobulins, in the treatment of AMR in KT, showing that the features of severe AMR are associated with graft loss.^{35,36}

In the present study, the ECP indications for the treatment of rejection were often related to the concomitant presence of cancers (18%) or infections (67%). This could be because such conditions usually lead to decreased immunosuppressive therapies, increasing

the risk of allograft rejection and not allowing for additional potentially deleterious immunosuppressant therapies.^{37,38} In such cases, ECP could be an interesting alternative treatment because of its immunomodulatory properties.³⁹ A recent study showed that KT recipients with cancer had a higher incidence of acute rejection and presented a dysfunction of natural killer lymphocytes (NK).³⁷ Interestingly, ECP-treated patients have been reported to have a higher frequency of NK cells than that in controls.⁴⁰ Furthermore, ECP has been demonstrated to promote Interleukin-1 β production, which synergizes with IL-2 to induce tumour-specific cytotoxic CD8+ T cells and plays a critical role in the priming of CD8+ T cell-mediated antitumour immunity by dendritic cells.⁴¹ Through these mechanisms, ECP may contribute to anti-tumoural immune responses. Limited data are available to support the role of ECP in immune responses to infections. However, in one study, ECP was used as a prophylactic treatment for allograft rejection in heart transplantation and was associated with a significant decrease in the plasma detection of CMV by PCR compared to that in the control group.¹⁶

Similar to the data in the literature, ECP was a relatively safe treatment in our study.²² Indeed, 79% of the patients had no side effects, and the majority of the reported side effects were not life threatening. The main complication reported was a tunnelled catheter-related infection (patient 30), which led to the interruption of ECP at 6.5 months. The incidence of catheter-related infections was 2.2/1000 catheter days, which is higher than the other reported rate in the literature (0.82/1000 catheter days).⁴² Therefore, vascular access could be a technical limitation, and ECP could be more easily administered to patients with a functional arterio-venous fistula.

This study has several limitations. Due to its retrospective nature and its long period of inclusion, the indications and applications of ECP treatment were heterogeneous, and there

was a lack of follow-up regarding the cancers and infections. In some cases, ECP failure may be explained by different factors. For instance, in the early 2000s, the Banff criteria were not discriminant for the AMR diagnosis, likely leading to insufficient rejection treatment and graft loss in 5 of the patients. Moreover, ECP was used as a rescue therapy, with a delayed initiation in a large proportion of the patients in our study: 24% of the patients began ECP with a serum creatinine level higher than the previously defined failure threshold of 412 $\mu\text{mol/L}$, 6 patients began ECP while they were dialysis-dependent, and the initial anatomopathological reports showed chronic damage. These factors could compromise the analysis of the impact of ECP. The anatomopathological data at ECP initiation were available for a large proportion of patients, and we showed that a high acute composite AMR score was a risk factor for graft loss. However, our sample size was too small to make any definitive conclusions about the other anatomopathological data, including chronic damage that is known to be predictive of graft loss.^{43,44} Moreover, we did not have follow-up data regarding the renal allograft biopsies during ECP therapy to assess their impact. Finally, ECP was used as a single therapy in only 5 patients (15%). Thus, the role of ECP in comparison to the other anti-rejection treatments that were used remains unclear.

In conclusion, our analysis highlighted the potential role of ECP in the target patient population of kidney allograft recipients with cellular or moderate antibody-mediated kidney allograft rejections and concomitant opportunistic infections or malignancies. ECP should be initiated as soon as possible because it is inefficient in cases of highly impaired kidney function, most likely due to severe chronic histological damage. The results of renal allograft biopsy should be taken into consideration. Further prospective trials are needed to clarify the indications for ECP in the treatment of kidney allograft rejection.

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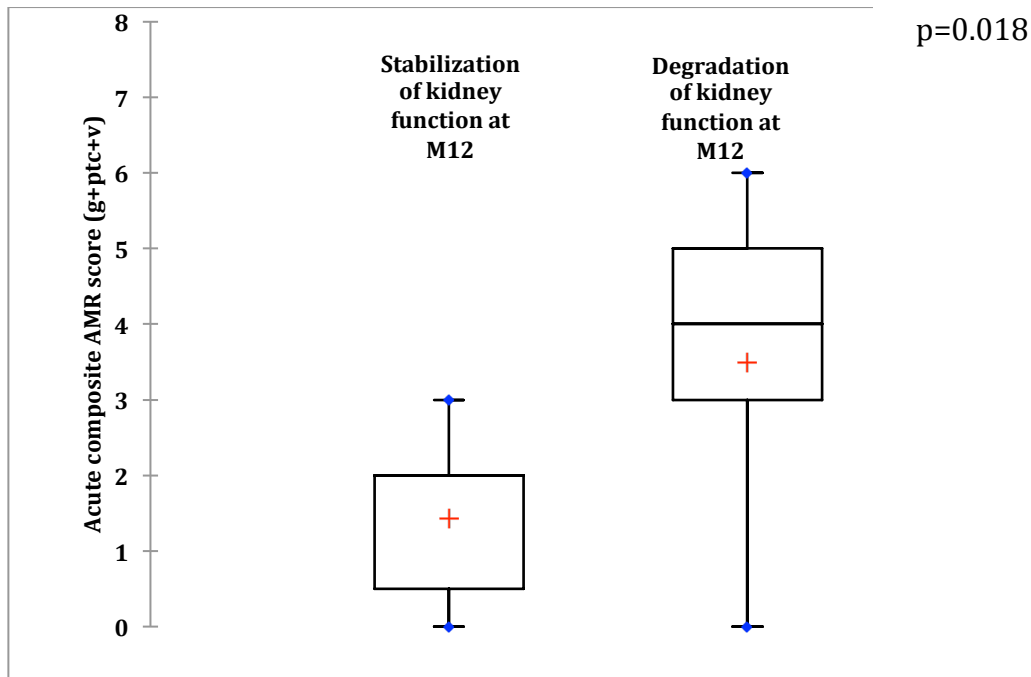
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A.



B.

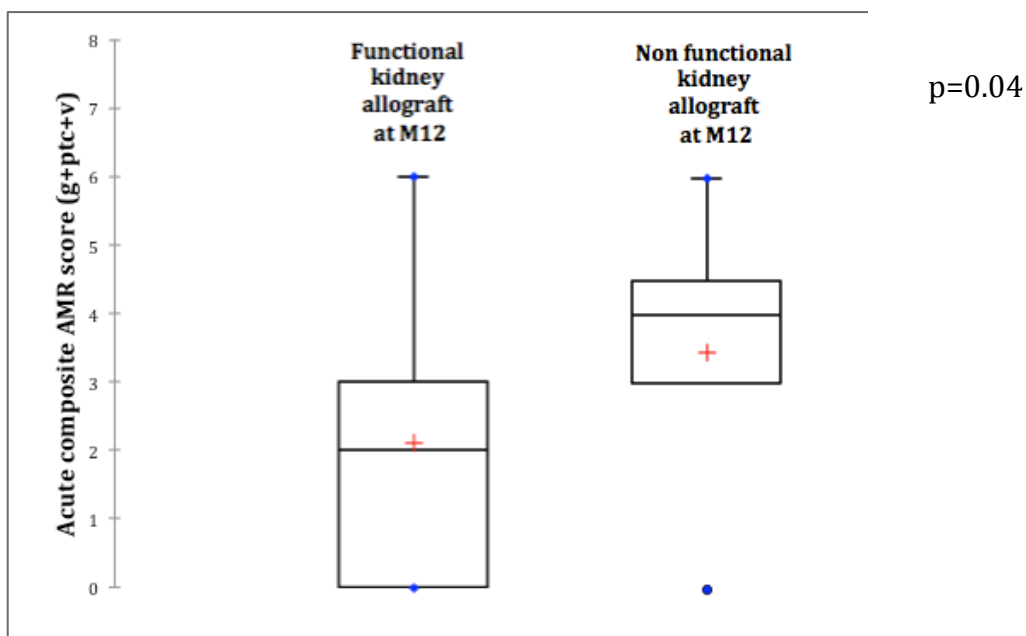


Figure 1. Impact of the acute composite antibody-mediated rejection score (sum of glomerulitis, peritubular capillaritis and intimal arteritis). A. On kidney function at 12 months after extracorporeal photopheresis B. On graft survival at 12 months after extracorporeal photopheresis. Box height indicates the IQR with the lower and upper edges of the box representing the 25th and 75th percentiles, respectively. The horizontal line is the median. The lower whisker represents the 25th percentile minus 1.5 times the IQR and the upper whisker the 75th percentile plus 1.5 times the IQR. Values outside the whiskers are outliers.

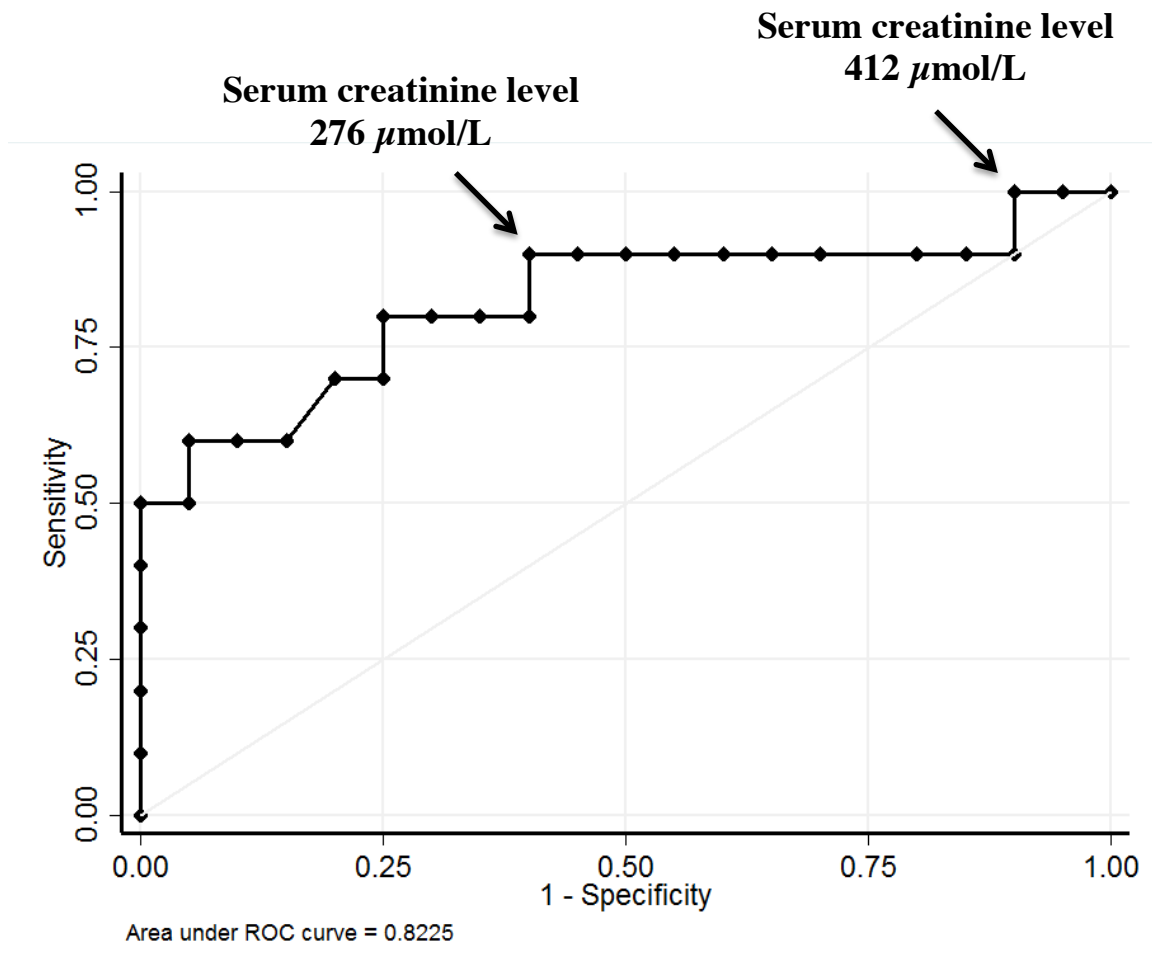


Figure 2. ROC-curve representing the probability of graft lost at M12 according to serum creatinine levels at extracorporeal photopheresis introduction

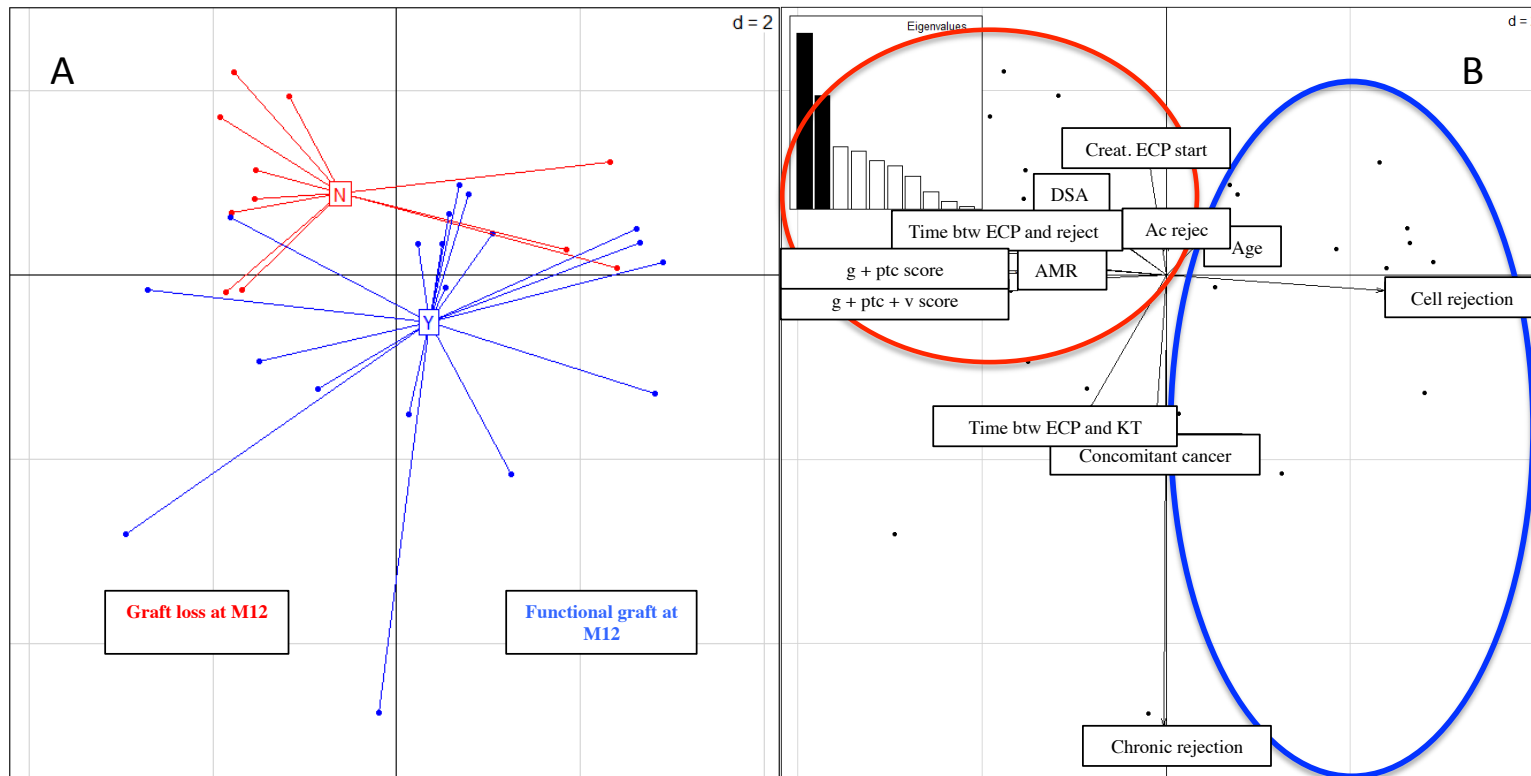


Figure 3. Results of factorial mixed data analysis. A: Patients representation showing 2 clusters: one with functional graft at M12 (Y, blue) another with graft loss at M12 (N, red). B: Variables representation showing 2 clusters : one with functional graft at M12 (blue) another with graft loss at M12 (red). Ac rejec: acute rejection ; AMR: antibody-mediated rejection; btw: between ; Creat: serum creatinine level ($\mu\text{mol/L}$) ; ECP: extracorporeal photopheresis ; reject: rejection.

Table 1. Patients' characteristics

	Number of patients (%)	Functional graft at M12	Non functional graft at M12
Age at transplantation (years)	48 (17-73)	50 [17-70]	43 [24-73]
Sex			
Female	11 (33%)	6 (30%)	5 (38%)
Male	22 (67%)	14 (70%)	8 (62%)
Donor type			
Deceased	31 (94%)	18 (90%)	13 (100%)
Living	2 (6%)	2 (10%)	0
Immunosuppressive therapies			
Induction			
Basiliximab	19 (61%)	12 (60%)	7 (54%)
Anti thymocyte globulin	13 (39%)	7 (35%)	6 (46%)
Maintenance			
Cyclosporin	16 (49%)	8 (40%)	8 (61%)
Tacrolimus	15 (45%)	10 (50%)	5 (29%)
mTOR inhibitor	2 (6%)	2 (10%)	0
Mycophenolate mofetil	27 (82%)	17 (85%)	10 (77%)
Azathioprin	5 (15%)	2 (10%)	3 (23%)
Mycophenolic acid	1 (3%)	1 (5%)	0
Corticosteroids	33 (100%)	20 (100%)	13 (100%)

Table 2. ECP indications and results.

Patient	Sexe / Age of KT (yrs)	Conc. inf. complications	Conc. cancer complications	Rejection treatment	Time btw rejection/ ECP (mth)	ECP duration (mth) / sessions number	Serum creat ECP initiation (µmol/L)	Serum creat M12 (µmol/L)	Total graft survival/ Graft survival after ECP (mth)
Acute	Antibody	Mediated	Rejection						
1	M / 64	N	Basocellular carcinoma	No treatment	8	10 / 17	273	325	91 / 24
2	M / 47	N	Lung and prostatic	No treatment	3	14 / 24	96	140	FG/f-up: 27
3	F / 47	Septicemia / CMV	N	No treatment	1	45 / 50	200	207	102 / 72
4	M / 43	N	N	MP	1	5 / 20	459	D	38 / 6
5	F / 27	N	Lymphoma	MP	1	2 / 7	242	212	136 / 48
6	F / 29	Pneumonia / CMV	N	MP	1	0.5 / 6	412	D	117 / 6
7	M / 63	Pneumonia / CMV	N	MP / IVIg	2	0.5 / 3	531	D	73 / 0.5
8	M / 52	Hepatic abscesses / CMV / BKV	N	MP / IVIg	3	6 / 23	150	177	FG/f-up: 78
9	F / 17	Pyelonephritis	Lymphoma	MP / IVIg	1	2 / 10	188	83	FG/f-up: 17
10	M / 25	N	N	MP / OKT3	1	67.5 / 60	411	277	72 / 66
11	M / 57	N	N	MP / OKT3	1	1.5 / 9	D	D	57 / 0
12	M / 52	Septicemia	N	MP / OKT3	25	4.5 / 21	223	530	47 / 18
13	F / 32	N	N	MP / ATG	4	11 / 29	450	D	21 / 11
14	M / 59	CMV	N	MP/ ATG	12	1 / 6	685	D	13 / 0.5
15	M / 44	N	N	ATG	13	2 / 7	202	210	57 / 37
16	M / 41	BKV / Pneumocystis	N	PEX / IVIg	1	1.5 / 14	176	264	FG/f-up:40
17	M / 34	N	N	MP / PEX / IVIg	11	2 / 17	149	D	102 / 7
18	F / 66	Peritonitis	N	MP / PEX / IVIg	10	4 / 28	279	D	31 / 12

Patient	Sexe / Age of KT (yrs)	Conc. inf. complications	Conc. cancer complications	Rejection treatment	Time Rejection / ECP (mth)	ECP duration (mth) / sessions number	Serum creat ECP initiation (µmol/L)	Serum creat M12 (µmol/L)	Total graft survival/ Graft survival after ECP (mth)
19	M / 41	Septicemia	N	PEX / IVIg	3	6 / 24	350	396	FG/f-up: 12
20	M / 20	CMV / EBV	N	MP / PEX / RTX	6	4 / 15	171	200	FG/f-up: 31
21	M / 42	BKV	N	MP / PEX / RTX / IVIg	21	0.5 / 4	D	D	26 / 0
22	M / 73	BKV	N	MP / PEX / RTX / IVIg	3	2.5 / 12	387	D	42 / 3
23	M / 70	CMV	N	MP/ ATG / RTX	2	1 / 7	270	200	FG/f-up: 12
24	M / 66	CMV / BKV	N	ATG / RTX / IVIg	2	3 / 12	340	285	FG/f-up: 15
Chronic	Antibody	Mediated	Rejection						
25	M / 48	N	Cut T cell lymphoma	No treatment	6	18 / 24	176	184	DFG 243 / 22
26	F / 59	Pyelonephritis / CMV	N	MP	2	current ECP	225	200	FG/f-up: 10
Acute	Cellular	Rejection							
27	F / 34	Septic shock / Pyelonephritis	N	No treatment	2	1.5 / 9	D	D	10 / 0
28	F / 66	CMV	N	MP	1	0.5 / 3	240	D	6 / 1
29	F / 66	N	N	MP	0.5	4 / 8	190	174	75 / 72
30	M / 70	CMV / EBV	Kaposi sarcoma	MP	1	6.5 / 30	146	200	FG/f-up: 16
31	M / 24	CMV	N	MP	3	3.5 / 7	340	D	9 / 2
32	M / 64	BKV	N	MP / ATG	6	2.5 / 13	358	380	39/33
33	F / 63	Pneumonia	N	MP / ATG / IVIg	4	6 / 10	337	ND	FG/f-up: 37

Abbreviations: btw: between, conc: concomitant, creat: creatinine D: dialysis, DFG: deceased with functional graft, FG : functional graft, f-up : follow-up, inf : infectious, IVig : intravenous immunoglobulines, MP : methylprednisolone pulses, N : no, ND : no dialysis, PEX : plasmapheresis

Table 3. Factors influencing extracorporeal photopheresis results at 12 months (M12)
A. Factors influencing results on kidney function B. Factors influencing results on graft survival

A.

	Stabilization of kidney function at M12	Worsening of kidney function at M12
	n=11 (33%)	n=22 (67%)
Age at KT (years)	53.5 [25-70]	45 [20-73]
Concomitant cancers	12.5%	15%
Concomitant opportunistic infections	62.5%	70%
Type of rejection: chronic	25%	0%
Type of rejection: acute	75%	100%
Type of rejection: cellular	12.5%	20%
Type of rejection: antibody-mediated	87.5%	80%
Acute composite score (t+v+i+g+ptc)	4 [2-8]	5.5 [2-9]
Acute composite AMR score (g+ptc+v)	2 [0-3] *	4 [0-6] *
Acute composite ACR score (i+t+v)	4 [0-8]	2 [0-8]
Chronic score (ci+ct)	2 [0-6]	2 [0-6]
Rejection treatment: ECP ± MP alone vs others	16.7%	29.4%
ECP duration (months)	6 [1-67.5]	3 [0.5-14]
ECP number of sessions	12 [7-60]	14.5 [3-30]
Time between rejection and ECP (months)	2 [1-13]	3 [1-25]

B.

	Graft loss at M12
	n=13 (39%)
Age of KT (years)	HR 1.00 [0.96-1.04]
Concomitant cancers	UD
Concomitant opportunistic infections	HR 0.64 [0.07-6.23]
Type of rejection: chronic	UD
Type of rejection: acute	UD
Type of rejection: cellular	UD
Type of rejection: antibody-mediated	HR 1.16 [0.25-5.48]
Acute composite score (t+v+i+g+ptc)	HR 1.33 [0.92-1.92]
Chronic composite score (ci+cg+ct+cv)	HR 1.39 [0.94-2.03]
Acute composite AMR score (g+ptc+v)	HR 1.44 [1.01-2.05] *
Acute composite ACR score (i+t+v)	HR 0.99 [0.76-1.29]
Rejection treatment: ECP ± MP alone vs others	HR 1.71 [0.48-6.09]
ECP duration (months)	HR 0.82 [0.63-1.06]
ECP number of sessions	HR 0.94 [0.87-1.01]
Time between rejection and ECP (months)	HR 1.00 [0.99-1.01]

Abbreviations: * p values less than 0.05 were considered statistically significant ; ACR : acute-cellular rejection ; AMR : antibody-mediated rejection ; ECP : extracorporeal photopheresis ; MP : methylprednisolone pulses ; UD : undefined. The results are presented as median and

interquartile range (A) and as hazard ratio (HR) and 95% confidence interval (B).

Table 4. ECP treatment in kidney transplantation: a review of the literature

Study Reference	Study Design	Number of patients	ECP indications	Previous therapies	ECP schedules	Results on kidney function
Transplant rejection treatment						
Sunder Plassman G <i>et al</i> , Lancet, 1995) ²⁴	Retrospective, monocentric	3	2 acute / 1 chronic rejections	MP + ATG or OKT3 for acute rejections	2s/2 wk during 4-8 mth	Follow-up 4-13 mth : 1 stabilization, 1 improvement for acute rejections / 1 decrease for chronic rejection
Horina JH <i>et al</i> , Lancet, 1995 ⁽²⁴⁾	Retrospective, monocentric	3	1 acute / 2 chronic rejections	OKT3	2 cons s/mth during 3 mth	3 graft failures
Baron ED, Photodermatol Photoimmunol Photomed, 2001 ⁽¹⁸⁾	Retrospective, monocentric	1	Acute rejection	OKT3	2 cons s/wk during 3 wk	Improvment . ELISPOT assay : increase of IL5-producing cells
Genberg H <i>et al</i> , Transplant Proceed, 2005 ⁽³⁵⁾	Retrospective, monocentric	7	Acute rejections	MP + ATG	2-3 s /wk with a total of 6-26s	Follow up 12 mth : 5 improvements, 2 stabilizations At last follow-up (12-43 mth) 7 functional grafts
Fernandez EJ, Nefrologia, 2015 ⁽³⁶⁾	Retrospective, monocentric	1	Acute rejection	MP + ATG	1 s/wk for 14 s associated to IVIg and 1 s/wk for 6s 9 mth later	Stabilization and decrease after the 1st treatment period, improvment after the 2nd treatment period
Dall'Amico R, JASN, 1998 ⁽³⁷⁾	Prospective, monocentric	3	Acute rejection	MP + OKT3	2 cons s/wk during 1 mth, then 2 cons s/2 wk during 2 mth, then 1 s/mth during 3 mth	2 stabilizations, 1 graft loss
Jardine MJ, Journal of Clinical Aphereis, 2009 ⁽²⁰⁾	Prospective, monocentric	10	Acute rejection	MP + ATG (9), OKT3 (1)	1 s/wk for a total of 5-12 s	Follow up 65 mth : 9 stabilizations, 1 graft loss by initial disease recurrence
Prophylactic treatment of transplant rejection						
Lamioni A, Transplantation, 2007 ⁽⁸⁾ ³⁶	Prospective, monocentric	2	Prophylactic treatment of rejection	CNI + MMF	2 s/wk during 3 wk	At 12 mth: no rejection, increase in Treg and decrease in TNF- α .
Kusztal M , Transplant Proceed, 2011 ⁹⁾ ³⁷	Prospective, monocentric	10	Prophylactic treatment of rejection	CNI + MMF	12-16s during the first 3 mth post transplantation	At 6 mth : significantly better kidney function and increase in Treg. Side effects : hypotension (2), increase of body temperature > 37.5°C (4), red blood cell loss due to technical problems (3)

Abbreviations: ATG: anti-thymocyte globulin, CNI: calcineurin inhibitors, cons: consecutive, MMF: mycophenolate mofetil, MP: methylprednisolone pulses, mth: months, OKT3: muromonab-CD3, s: sessions, wk: week