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EXTRACORPOREAL PHOTOPHERESIS IN PROPHYLAXIS OF RENAL TRANSPLANT REJECTION

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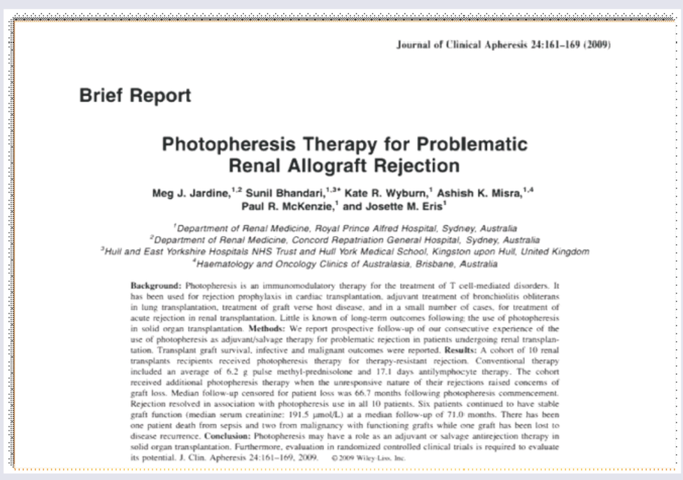
There is an acute graft rejection in 20% of recipients after renal transplantation in the early postoperative period.
The acute rejection remains the most serious problem and the one of the main causes of graft loss in both early and late postoperative period.
The acute rejection reactions number and severity has a direct correlation with nephrons mass loss transplant survival.
Modern immunosuppression is nonspecific and increases the risk of infection.
Drugs that suppress the immune response to allografts, do not generate immunological tolerance to transplant.

Extracorporeal photopheresis (ECP) was proposed in 1987 by a team of researchers at Yale University for therapy of T-cell skin lymphoma.
Application of this method in patients with T-cell skin malignant lymphoma leds to increase twice in median survival.
Currently, this method of treatment is used in about 200 largest medical centers in the world .



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Brief Report

Photopheresis Therapy for Problematic Renal Allograft Rejection

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Background: Photopheresis is an immunomodulatory therapy for the treatment of T cell-mediated disorders. It has been used for rejection prophylaxis in cardiac transplantation, adjuvant treatment of bronchiolitis obliterans in lung transplantation, treatment of graft verse host disease, and in a small number of cases, for treatment of acute rejection in renal transplantation. Little is known of long-term outcomes following the use of photopheresis in solid organ transplantation. **Methods:** We report prospective follow-up of our consecutive experience of the use of photopheresis as adjuvant/salvage therapy for problematic rejection in patients undergoing renal transplantation. Transplant graft survival, infective and malignant outcomes were reported. **Results:** A cohort of 10 renal transplants recipients received photopheresis therapy for therapy-resistant rejection. Conventional therapy included an average of 6.2 g pulse methyl-prednisolone and 17.1 days antilymphocyte therapy. The cohort received additional photopheresis therapy when the unresponsive nature of their rejections raised concerns of graft loss. Median follow-up censored for patient loss was 66.7 months following photopheresis commencement. Rejection resolved in association with photopheresis use in all 10 patients. Six patients continued to have stable graft function (median serum creatinine: 191.5 μmol/L) at a median follow-up of 71.0 months. There has been one patient death from sepsis and two from malignancy with functioning grafts while one graft has been lost to disease recurrence. **Conclusion:** Photopheresis may have a role as an adjuvant or salvage antirejection therapy in solid organ transplantation. Furthermore, evaluation in randomized controlled clinical trials is required to evaluate its potential. J. Clin. Apheresis 24:161–169, 2009. © 2009 Wiley-Liss, Inc.

10 recipients with recurrent renal transplant rejection
resistant to all kinds of therapy (methylprednisolone, antithymocyte globulin)

After application ECP rejection was suppressed in all 10 patients. 6 patients have a stable graft function during 71 months. 3 patients subsequently died because of nonephrological diseases,
1 patient has graft loss due to recurrent glomeluronephritis. Repeated rejection was not observed

ECP may be an adjuvant therapy or as a method of choice for the prevention of rejection in organ transplantation

Application of the ECP in patients after renal transplantation can improve graft function and reduce risk of rejection.
The mechanism of action ECP after renal transplantation is not completely understood

Primary aim: evaluate the efficacy of ECP in preventing of acute graft rejection.
Secondary aim: determine the ECP mechanism of action.

Material and methods. It was a comparative prospective study that included 40 patients after renal transplantation.
There was 2 groups: G1 – with ECP and G2 with a standard therapy. Immunosuppressive therapy included calcineurin inhibitors - tacrolimus, mycophenolate, and corticosteroids. Induction therapy was a monoclonal anti-CD25 antibodies and methylprednisolone.
In each G1 patients was performed a 15 ECP treatments in 6 month with special scheme.

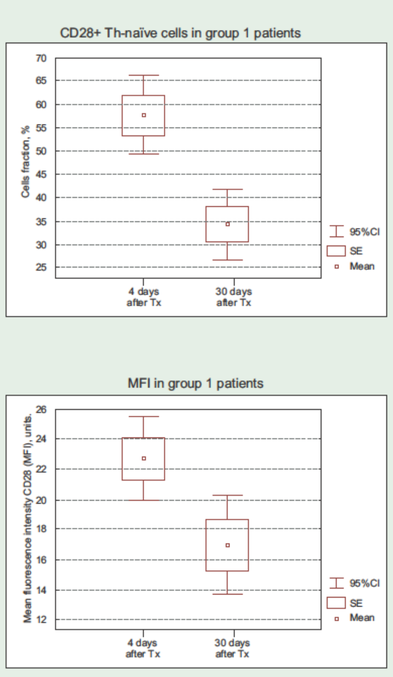
In G1 diuresis recovering was faster (median: G1 – day 5, G2 – day 8) .
A month after the Tx in G2 GFR was 36,1 ± 17 ml / min, in G1 - 59,6 ± 23 ml / min.
The difference in GFR between the groups at 6 months increased more and became statistically significant (p = 0,006).

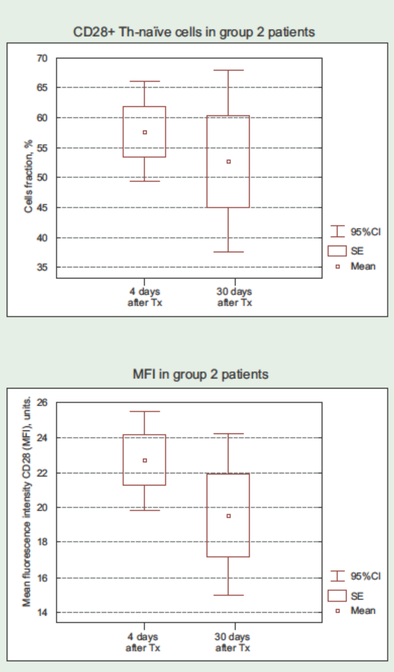
Parameter		Main group, (n = 15)	Comparison group, (n = 15)	P
Blood Urea, mmol / l	30 days	15,2±8,8	14,4±5,8	>0,05
	180 days	12,4±4,6	15,3±9,4	>0,05
Blood creatinine, mmol / l	30 day	0,22±0,1	0,17±0,06	>0,05
	180 days	0,15±0,06	0,2±0,1	>0,05
Glomerular filtration rate in, ml/min	30 days	55,2±33	36,1±17	>0,05
	180 days	**59,6±23**	**31,5±11,7**	**0,006***
Daily proteinuria, g /day	30 days	0,92±0,8	0,92±0,7	>0,05
	180 days	0,3±0,06	0,51±0,4	>0,05

The mechanism of ECP.

There was a significant decrease of number CD28+ Th-naïve cells and mean fluorescence intensity (MFI) in G1 patients.

At the same time, there was no significant change of the number of CD28+ Th-naïve cells and also no change of mean MFI in G2 after 1 month after Tx.





We can explain this fact. Ammifurin molecule having high avidity for pyrimidine nucleobases and intercalates between DNA thymine and primary mRNA uracil. As result of formation of strong cross links, mRNA transcription process can be interrupted, which reduces the translation of the protein. As a result ECP was disturbed synthesis of actively synthesizing molecules - especially the CD28.
In the absence of the signal generated by receptor CD28 naive CD4+ cells forming Th1- phenotype with negative regulation of cytokines - mediators of cell and humoral response.
The absence of a costimulatory signal leads to the clonal anergy and the induction of molecules associated with apoptosis.

Conclusion: ECP can be considered as a tolerance process inductor after renal transplantation.
ECP is effective adjuvant therapy for prevention and treatment of renal graft rejection.

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