EXTRACORPOREAL PHOTOPHERESIS AS INDUCTOR OF PARTIAL IMMUNOLOGICAL TOLERANCE IN RENAL TRANSPLANTATION

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INTRODUCTION

Extracorporeal photopheresis (**ECP**) is an effective method of resistant transplant rejection management. This method is widely used in renal, heart, and lung transplantation. In terms of renal transplant rejection prevention this method and its mechanism of action is not studied well enough.

It is known that interaction of CD28, CTLA-4 molecules with their CD80/86 ligands during co-stimulation is a key factor of both induction and suppression of immune response in total Fig. 1.

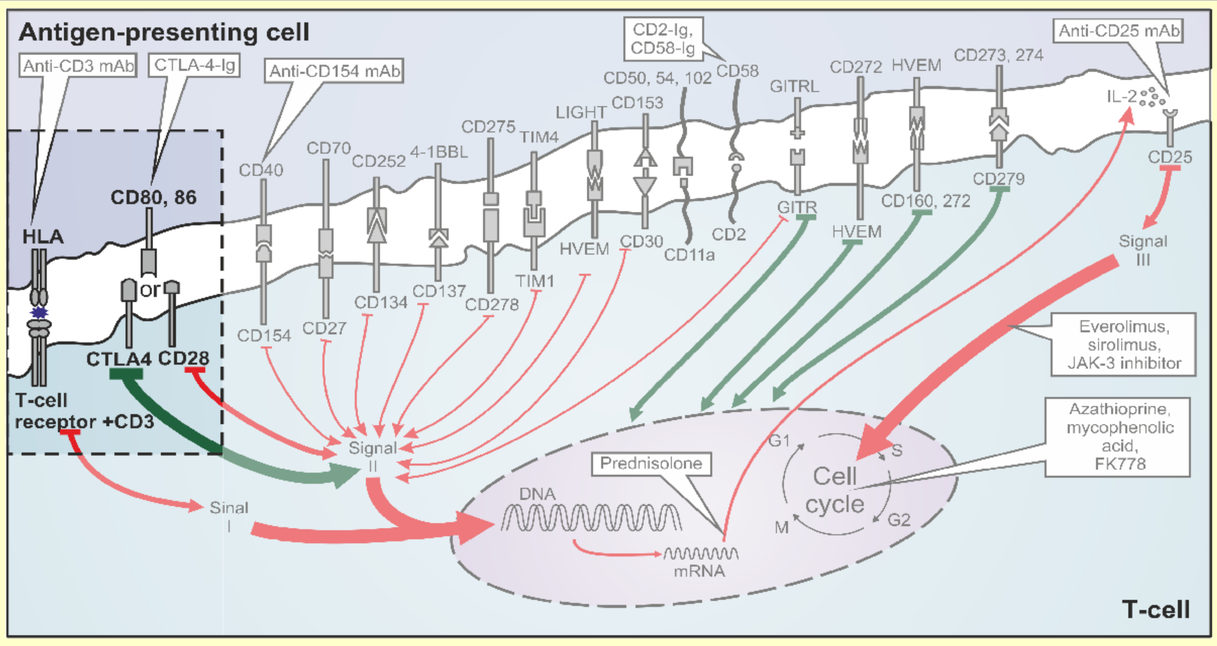

Figure 1. Activation and costimulation of T cells. **Activation signal. Iinhibitory signal**

OBJECTIVES:

to study both the mechanism of action of **ECP** and its influence on frequency of rejection episodes and renal transplant function.

METHODS

A prospective randomized study in 24 pairs of recipients has been conducted. One donor kidney was transplanted to a patient of the main group, the other – to the patient of the control group. The main group was treated with the following immunosuppressive therapy: tacrolimus, mycophenolate mofetil, prednisolone combined with 15 sessions of **ECP**; control group received immunosuppressive therapy only.

A percent (%) of naïve T-helpers expressing CD28 (CD3+CD4+CD27+CD28+CD45RO- phenotype) and mean fluorescence index (MFI) of the molecule were investigated. These parameters were assessed in healthy people, in the main and control groups on 4th and 30th day after transplantation. As well as this on 30th and 180th day after transplantation the following parameters were estimated: daily proteinuria, serum creatinine and glomerular filtration rate (GFR). Statistical analysis: repeated measures ANOVA with a posteriori Tukey test.

We studied the number of rejection episodes and infectious complication in these groups during 6 months. The protocol biopsies were performed on the 30th and 180th day.

RESULTS

In healthy people CD28 molecule is present on the whole surface of naïve T-helpers pool – fig. 2. However, its MFI is greatly variable. In recipients of renal transplant on 4th day after transplantation CD28+Th and MFI decrease significantly. MFI of CD28 molecules of naïve T-helpers decreases proportionally to the number of these cells: r=0.58, p=0.01.

Patients in control group on 30th day after transplantation had no significant changes in percent of T-helpers expressing CD28, (p=0.42), and MFI (p=0.087). In the main group on 30th day a significant decrease in percent of CD28+Th (p<0.001) and MFI (p<0.001) was observed in relation to the parameters on 4th day after transplantation. The number of CD28+Th in patients of the main group was statistically different from that of control group (p<0.001). This dynamics in patients of the main group against the background of extracorporeal photopheresis can be indicative of a specific and universal inhibition of expression of co-activating molecules on naïve T-helpers. Also in the main group the number of CD8 cells on 30th day was significantly lower than that on 4th day, as well as in control group - fig. 3.

Clinical outcomes (fig. 4). 1 month after transplantation patients of the main group had lower daily proteinuria values , after 180 days – lower daily proteinuria, serum creatinine values and higher GFR versus control group.

In the main group during 6 months after transplantation there were no rejection episodes, in the control group there were 4 episodes (IA, IB, IIB, III - Banff 2005). Frequency of infectious complications in the main group was twice lower (8 vs. 17).

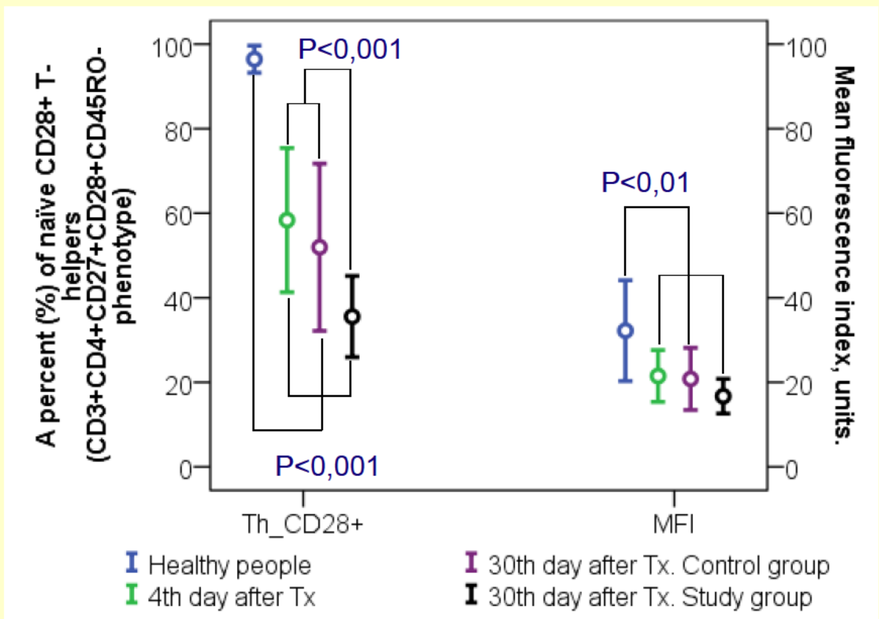

Figure 2. A percent of CD28+ naïve T-helpers and MFI.

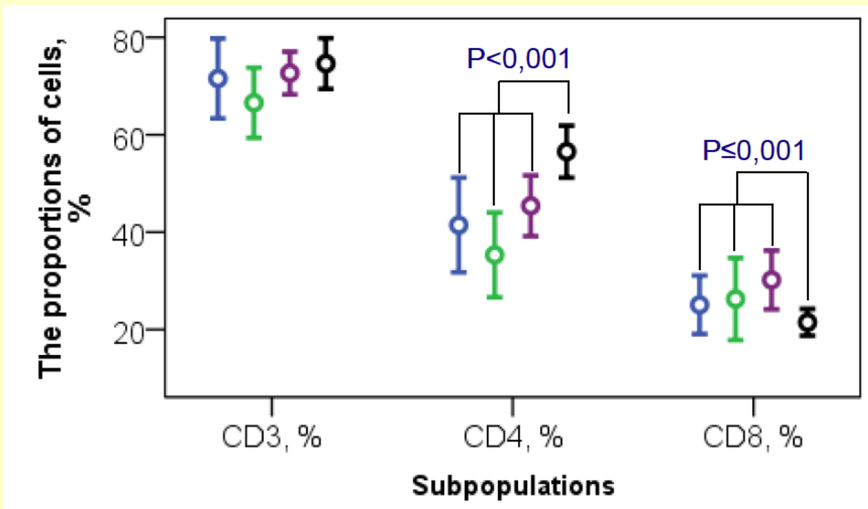

Figure 3. Lymphocyte subpopulations

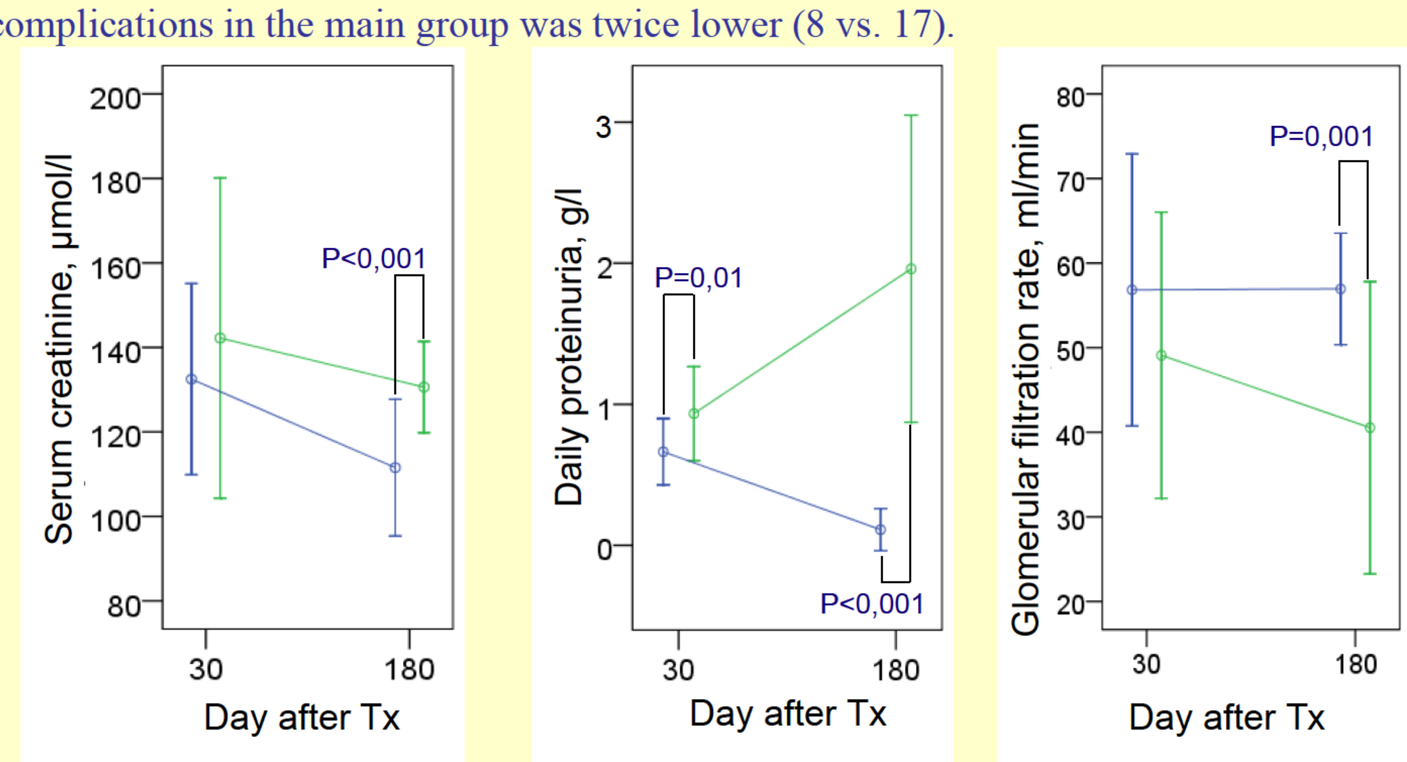

Figure 4. Clinical outcomes. **Main group. Control group.**

CONCLUSIONS

ECP is an effective method of transplant rejection prevention. This method helps to decrease the number of rejection episodes and improve transplant function. ECP is an inductor of partial immunological tolerance to transplant. The study assessing long-term outcomes is in progress.

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