

EVEROLIMUS AND LOW DOSE OF TACROLIMUS COMBINED WITH THYMOGLOBULIN INDUCTION INDUCES REGULATORY T CELLS EXPANSION IN DE NOVO KIDNEY TRANSPLANT RECIPIENTS: PRELIMINARY DATA OF CONTROLLED RANDOMIZED STUDY (EVER TWIST)

Carmelo Libetta ¹, Elisabetta Margiotta ¹, Ilaria Boretta ¹, Michele Canevari ¹, Claudia Martinelli ¹, Elisa Lainu, Massimo Abelli ¹, Federica Meloni ², Vincenzo Sepe ¹ and Antonio Dal Canton ¹.

¹, Unit of Nephrology, Dialysis and Transplantation, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy, 27100 and ², Unit of Pneumology, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy, 27100.

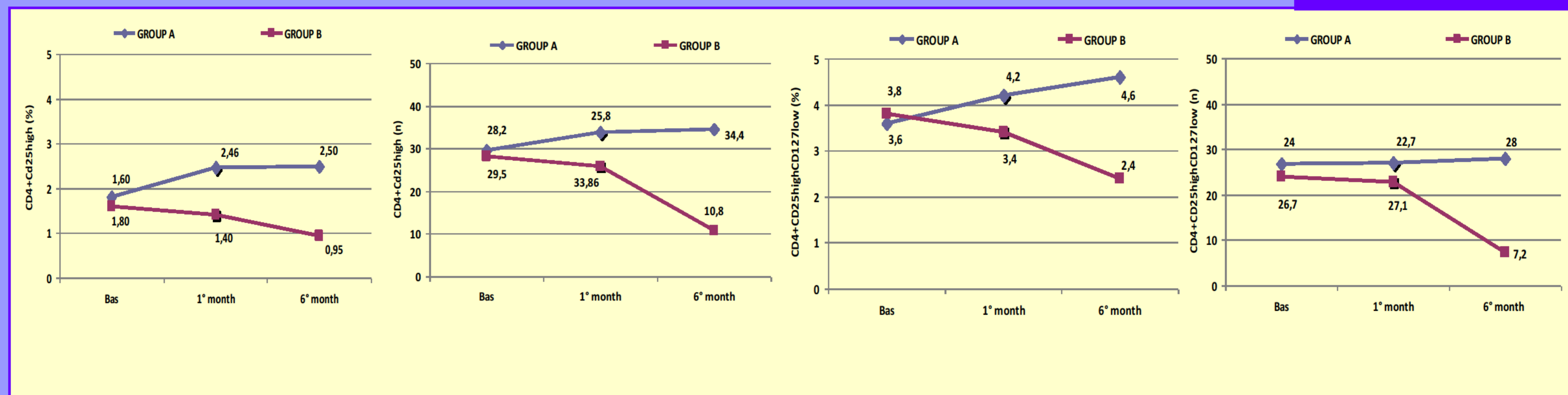
Objectives:

Immunosuppressive drugs are essential for the prevention of acute transplant rejection, but they probably also prevent tolerance. Among lymphoid cells the regulatory T cells (T reg) play a central role in the balance between tolerance and immunity as they are responsible of peripheral tolerance. Aim of this clinical trial is to evaluate the effect of different immunosuppressive regimens on T-reg cells.

Methods:

According to Calne's "window of opportunity for immunologic engagement" concept to favour tolerance, we have designed a prospective, randomized, open-label clinical trial in which de novo renal transplant recipients will be randomized according to: a) a new immunosuppressive protocol (group A) that after induction with methylprednisolone (M) and Thymoglobulin (ATG) dosage 2.5 mg/kg, immunosuppression is interrupted for 72 hrs, and resumed with tacrolimus (low-dose)+ Everolimus +Mycophenolate sodium (MPS, withdrawal at 6^o month)+ M (withdrawal at 1^o month); b) standard arm (group B) induction with ATG and maintenance with Tacrolimus+MPS+M. Up to the present we have recruited 31 patients (14 males and 17 females): 15 in the group A and 16 in the group B. On enrollment blood samples were collected before the transplant (BAS) and at 6 month after kidney transplantation (Tx 6mo). The frequency of CD4+Cd25high and CD127- T-cells was determined by Fluorescence Activated Cell sorter (FACS) analysis.

Results:



Conclusions:

These preliminary data suggest that after 6 months, T-reg in patients of group A are significantly increased when compared both to the BAS and group B, while T-reg cells are suppressed by standard immunosuppressive therapy (group B). These results suggests that sperimental immunosuppressive protocol in vivo may improve peripheral tolerance in kidney transplant recipients.

References:

1. Kang SM, Tang Q, Bluestone JA, CD4(+)CD25(+) regulatory T cells in transplantation: progress, challenges and prospects, Am J Transplant, 2007, 7:1457-1463.
2. Spoerl S, Li XC, Regulatory T cells and the quest for transplant tolerance, Discovery Medicine, 2011, 56:25-34.
3. Gershon RK, Kondo K, Cell interactions in the inductions of tolerance: the role of thymic lymphocytes. Immunology, 1970, 18:723-737.
4. Toda A, Piccirillo CA, Development and function of naturally occurring CD4+CD25+ regulatory T cells, Journal of Leukocyte Biology, 2006, 80:458-470.
5. Thornton AM, Donovan EE, Piccirillo CA, Shevach EM, Cutting edge: IL-2 is critically required for the in vitro activation of CD4+CD25+ T cell suppressor function, J Immunol, 2004, 172:6519-6523.
6. Nelson BH, IL-2, regulatory T cells, and tolerance, J Immunol, 2004, 172:3983-3988.
7. Velthuis JH, Mol WM, Weimar W Baan CC, CD4+CD25bright+ regulatory T cells can mediate donor nonreactivity in long-term immunosuppressed kidney allograft patients, Am J Transplant, 2006, 6:2955-64.
8. Braudeau C, Racape M, Giral M, Louis S, Moreau A, Berthelot L, Heslan M, Ashton-Chess J, Soullillou JP, Brouard S, Variation in numbers of CD4+CD25highFoxP3+ T cell with normal immuno-regulatory properties in long-term graft outcome, Transpl Int, 2007, 20:845-55.
9. Louis S, Braudeau C, Giral M, Dupont A, Moizant F, Robillard N, Moreau A, Soullillou JP, Brouard S, Contrastino CD25hiCD4+ T cells/FoxP3 patterns in chronic rejection and operational drug-free tolerance, Transplantation, 2006, 81:398-407.

