

Abstract Type : Oral Presentation
Abstract Submission No. : F-008092

Phase 1/2 Donor Antigen Specific Treg Based Cell Therapy Clinical Trial To Induce Operational Tolerance In Living Donor Liver Transplant Patients

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Introduction: Selective immunosuppression to the recipient T cells responding to the donor graft antigen and maintain immune system necessary for homeostasis would be ideal strategy for the transplant patients. And sustain tolerogenic status to the graft despite cessation of immunosuppressant would minimize the risk of adverse life-threatening events related with the medication such as de novo cancer and cardiovascular disease. Our donor specific regulatory T cell-based therapy, successfully prove the therapeutic concept to achieve long term graft survival without any immunosuppressant in living donor liver transplant in single center, in which seven patients out of 10 have been achieved stable clinical graft function without any signs of pathological rejection over 10 years.

Methods: Based on the previous liver transplant tolerance clinical study, we have developed the GMP manufacturing process and delivery system as well as raw materials suitable for Japanese pharmaceuticals regulation. During the manufacturing process, PBMC from transplant recipient were mixed with irradiated donor PBMC in the presence of anti-human CD80 and CD86 mAbs to induce donor antigen specific Treg based cell product. Clinical protocol of safety and efficacy to induce liver transplant tolerance were also agreed with the Japanese regulation to start clinical trial as phase 1 and 2.

Results: We have been conducting a single-arm, open-label, four transplant center clinical trial employing autologous donor antigen reactive Treg based suppressor T cells product in adult HLA mismatched living donor liver transplant recipients. This trial is composed of two phase: phase 1 as safety cohort (n=3) and phase 2 (n=7) as efficacy cohort with step-wise weaning and withdrawal of immunosuppression in 18months after transplant. Endpoints include safety and operational transplant tolerance over a year.

Conclusion: This trial, which is currently recruiting, will provide clinical evidence of safety and efficacy of our antigen specific Treg based product to induce liver transplant tolerance.