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Sponsor: Sanofi **Drug substance(s):** Rabbit Anti-thymocyte Immunoglobulin	**Study Identifiers:** U1111-1178-5402, NCT03099122 **Study code:** THYMOL07282

Title of the study:

A Prospective, Multi-center, Single-arm, Interventional Study of Thymoglobuline® Induction Therapy in Adult Recipients of Donated after Cardiac Death Kidney Transplant in China

Study center(s):

9 centers participated in this study.

Study period:

Date first participant enrolled: 30/Aug/2017

Date last participant completed: 27/Mar/2020

Study Status: Completed

Phase of development: IV

Objectives:

Primary Objective

Investigated the efficacy of the standard dose of Thymoglobuline® induction therapy for preventing acute rejection (AR) at 6 months after transplantation among recipients of Donated after Cardiac Death (DCD) kidney transplant

Secondary Objective(s)

1) To evaluate delayed graft function (DGF), graft survival and patient survival at 6 months after kidney transplant

2) To evaluate adverse events of Thymoglobuline® throughout the study until 6 months post- transplantation

3) To explore possible risk factors of AR and DGF in patients with DCD kidney transplant

4) To evaluate AR and DGF under different risk stratifications and explore an description optimal induction therapy regimen for recipients of DCD kidney transplant

Methodology:

This study was a prospective, multi-center, single-arm study of DCD kidney transplant recipients receiving Thymoglobuline® for induction therapy. Approximately 9 centers participated in this study. All patients were recipients of kidney transplant and then were followed for 6 months on an outpatient basis.

All patients were given Thymoglobuline® induction therapy with a standard cumulative dose of 5.0 mg/kg. The allowed variable interval for dosing was ±2.0 mg/kg.

Number of Participants:

Planned: 200

	Enrolled: 98
	Treated: 115
Evaluated:	
	Efficacy: 107
	Safety: 115

Diagnosis and criteria for inclusion:

Inclusion criteria:

1) Male or female

2) Patient was a Chinese recipient of kidney transplant for the first time

3) Patient was a recipient of kidney allograft from Chinese donors donated after cardiac death (including kidney donated after brain death followed by circulatory death)

4) Recipient's age was between 18 to 65 years old (including 18 years)

5) Donor's age was more than 5 years old

6) Recipient's weight was greater than or equal to 50 kg but less than or equal to 80 kg

7) Patient fully understood the study and signed the informed consent form (ICF) prior to any study procedure

Exclusion criteria:

1) Patient was a multiple organ transplant recipient

2) Recipient with previous kidney or other organ transplant history

3) Recipient and donor had incompatible blood types

4) Recipient and donor had 5 or 6 mismatched human leucocyte antigen (HLA)

5) Recipient was known to have an active infection or active chronic infection, or was seropositive for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV Ab), or human immunodeficiency virus (HIV). (Serological test results within 12 months before transplantation are acceptable.)

6) Recipient with cytomegalovirus (CMV) IgG negative who receives an allograft from CMV IgG positive donor (CMV IgG (D+/R-))

7) Recipient with any systemic infection requiring continuous treatment at enrolment, but prophylactic treatment of CMV and/or Pneumocystis carinii pneumonia (PCP) was allowed

8) Recipient had severe thrombocytopenia or leucopenia before operation (platelet count <75,000/ul, or the number of white blood cells <3,000 cells/mm3)

9) Serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST) or gamma glutamine transferase (GGT) ≥3ULN (upper limit of normal) within 1 week before transplantation, and not normalized at time of transplantation

10) Recipient had a history of malignancy within 5 years

11) Recipient with history of allergy and anaphylaxes to rabbit proteins or to any excipients

12) Recipient had known contraindications to the administration of Thymoglobuline®

13) Recipient had taken other investigational drugs or prohibited therapy for this study within 1 month or 5 of half-lives from screening, whichever was longer

14) Recipient had previously used Thymoglobuline®, or had participated in any clinical trial of any other medicine or device within 30 days before signing ICF.

15) Pregnant or lactating women

16) Male and female patients did not agree to practice medically acceptable contraception (i.e., barrier or pharmacologic: male patient must use condoms or his female partner must take oral contraceptives; the male partner of a female patient must use condoms) for at least 6 months following the study treatment.

17) Conditions/situations such as:

• Recipient not suitable for participation, whatever the reason, as judged by the Investigator, including medical, clinical, or psychosocial conditions, or patient potentially at risk of noncompliance to study procedures.

• Donor known or suspected to have active infection before donation (such as blood cultures positive, seropositive for hepatitis B surface antigen (HBsAg), or antibody against hepatitis C virus (HCVAb), or human immunodeficiency virus (HIV)) or hypersensitive recipients (eg. PRA positive) before transplantation, judged by the Investigator.

Study Products:

Investigational medicinal product: Rabbit Anti-thymocyte Immunoglobulin (Thymoglobuline®)

Route(s) of administration: Intravenous infusion

Dose regimen: Cumulative dose 5.0 ±2.0 mg/kg, with daily dose 1-1.5 mg/kg/d, 3-6 days (no more than 7 mg/kg of cumulative dose)

Non investigational medicinal products

Induction therapy:

Methylprednisolone (500 mg/day, intravenously) was given prior to oral administration as induction therapy, according to local institutional practice.

Maintenance immunosuppression therapy:

- Tacrolimus: Initial dosage was 0.1- 0.15 mg/kg/d, and could be adjusted to achieve target therapeutic trough levels in peripheral blood (i.e. TAC C0 5-10 ng/ml during 0- 3 months, TAC C0 4-8 ng/ml during 3-6 months). Initiation could be delayed depending on the Investigator's judgment according to the patient's recovery of renal function.
- MPA: Initial dosage was Mycophenolate mofetil 1500-2000 mg/d or Mycophenolate Na 1080-1440mg/d, and adjusted to maintenance dose (Mycophenolate mofetil 1000- 1500mg/d or Mycophenolate Na 720-1080mg/d) by 3 months post operation. The dose modifications would be determined by doctors according to patients' clinical requirement.
- Oral administration of prednisone following IV Methylprednisolone would be tapered to a maintenance dose of 5-10 mg/day, dose modifications according to patients' clinical requirement decided by doctors.

Recipients must be given ganciclovir or valganciclovir for CMV prophylaxis for at least 12 weeks unless there was a special case. Sulfamethoxazole plus trimethoprim must be given orally for at least 12 weeks for pneumocystis carinii pneumonia (PCP) prophylaxis.

Bacterial and fungal prophylaxis were required at least 1 week after transplantation, dose and duration would be according to patients' clinical requirement decided by doctors. For any patient who experienced AR, the Investigator could choose any treatment regimen thereafter and it would be recorded for observation until 6 months post-transplantation.

Duration of participation: 6.5 months **Duration of observation:** All patients were followed 6 months after kidney transplant, patients who experienced acute rejection continued to be followed up for 6 months.
Criteria for evaluation: **Primary endpoint:** The incidence of biopsy-proven acute rejection (BPAR) at Month 6 after DCD kidney transplant among recipients receiving standard dose of Thymoglobuline®. **Secondary endpoints:** 1) The incidence of DGF and duration of DGF 2) Graft survival and patient survival at 6 months post- transplantation 3) The incidence of infection, leucopenia, thrombocytopenia, malignancies at 6 months post- transplantation 6 4) Possible risk factors of AR/DGF in recipients of DCD kidney transplant 5) The incidence of AR and DGF under differential risk stratification
Statistical methods: The study was to evaluate the incidence of biopsy-proven acute rejection (BPAR) at Month 6 after DCD kidney transplant in recipients receiving standard dose of Thymoglobuline®. BPAR was summarized descriptively and number of subjects with BPAR and the percentage were presented, as well as the 2-sided 95% exact CI. Kaplan-Meier survival analysis was performed to estimate the time from kidney transplantation to occurrence of AR, with which, a KM curve was prepared. AR was summarized using the same method. The diagnosis time, results, basis, as well as the treatment and prognosis of AR/BPAR were tabulated. All statistical procedures were completed using SAS version 9.4. Full analysis set (FAS): a set of patients who receive at least one dose of the investigational drug, except for those failing to meet major entry criteria and dropouts. All efficacy analysis was based on FAS, unless otherwise specified. Safety set (SS): a set of patients who receive at least one dose of the investigational drug. Safety analysis was based on SS. Analysis for this study mostly was descriptive. For continuous variables, this included the number of observations (missing data), mean, median, standard deviation, minimum, and maximum. Decimal points shall be consistent with that recorded in the CRF for minimum and maximum.
Summary Results: **Population characteristics:** A total of 117 subjects were screened in this study, 115 of them received at least one dose ofThymoglobuline®. Among them,107 subjects were included into the full analysis set, the 107 subjects in FAS completed the treatment, among which, 102 subjects completed the study and 5 subjects prematurely discontinued the study. The primary causes of recipient's end-stage renal disease was glomerulonephritis [43 recipients (50.6%)]. 102 recipients (95.3%) used alternative therapies before transplantation, while the other 5 recipients (4.7%) did not. Among the 107

recipients, 105 were HLA mismatched. 1, 2, 3, 4 HLA mismatches were observed respectively in 7 recipients (6.5%), 36 recipients (33.6%), 36 recipients (33.6%) and 26 recipients (24.3%).97 recipients (91.5%) were negative for PRA, while 9 recipients (8.5%) were positive.

As for the 107 donors, 39 of the 107 donors (36.4%) fell in category of DCD and 68 of the 107 donors (63.6%) fell in category of DBCD. The mean cold ischemia time was 6.54 h, mean time from systolic blood pressure < 50 mmHg was 11.4 min, mean time from withdrawal of life support was 19.0 min, and mean time from cardiac arrest was 6.1 min.

Efficacy:

For the 107 subjects in FAS, a total of 3 subjects (2.8%) had BPAR at Month 6 post-transplantation; 5 subjects (4.7%) had AR(including BPAR), and the AR incidence and 95% CI estimated by KM method was 4.7 (2.0%, 11.0%)

In terms of the secondary efficacy endpoints, a total of 14 subjects (13.1%) had DGF at Month 6 post-transplantation, with a mean duration of 19.19 days.

Safety results:

A total of 93 subjects (80.9%) had TEAE during the study, among which, 14 subjects (12.2%) had severe TEAE, 53 subjects (46.1%) had study drug related TEAE, 1 subject (0.9%) had TEAE resulting in discontinuation of Thymoglobuline® treatment, 21 subjects (18.3%) had SAE, and 1 subject (0.9%) died of septic shock within 1 month after transplantation. No subject had TEAE or AESI resulting in withdrawal from the study.

As estimated by KM method, graft survival, patient survival, and the incidence of infection, leucopenia, thrombocytopenia, malignancies with the 95% CI were: 97.2% (91.5%, 99.1%), 99.1% (93.5%, 99.9%), 22.6% (15.8%, 31.8%), 9.6% (4.9%,

16.5%), 13.0% (7.5%,20.6%) and 0.9%(0.0%, 4.7%).respectively.

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