Sequential Transplantation of Umbilical Cord Blood Stem Cells and Islet Cells in Children and Adolescents with Monogenic Immunodeficiency Type 1 Diabetes Mellitus

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Background

Children diabetes mellitus have an early onset, a long course of disease, many acute and chronic complications, high disability and mortality. And intensive studies of its etiology and pathogenesis are the focus and hotspot.

Type 1 diabetes mellitus (T1DM) could be divided into immune-mediated T1DM and monogenic immunodeficiency T1DM. Immune-mediated T1DM is closely related to HLA, which is triggered by environmental factors such as infection. With the popularization of gene sequencing, especially the second generation sequencing, children with monogenic immunodeficiency T1DM can be isolated, such as immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX syndrome) caused by FOXP3 mutation.

The monogenic defect is often accompanied by persistent and progressive aggravation of multi-organ damage, which not only leads to the corresponding organ dysfunction, but also requires continuous additional intervention and treatment, resulting in huge medical costs. but it is often difficult to avoid the poor outcome of early death. For example, FOXP3 mutation leads to the loss of regulatory T cell function and the inactivation of the key protein Scurfin, which controls T cell activation. Hemorrhage, sepsis, colitis or diabetes complications caused by IPEX syndrome can lead to early death in children.

Early diagnosis and stem cell transplantation can lead to immune reconstitution, avoid the risk of organ toxicity and chronic immunosuppression-related infections, and may prevent autoimmune endocrine organ damage. While continuous advances in islet

transplantation technology provide a basis for radical treatment of T1DM in children caused by monogenic immunodeficiency.

Objectives

To cure monogenic immunodeficiency T1DM, we combine the umbilical cord blood stem cell transplantation and islet cell transplantation together. We plan to correct immune deficiency by umbilical cord blood stem cell transplantation and transplant human islet cells after stable condition in order to correct secondary damage of immune deficiency and hyperglycemia, and finally achieve the goal of long-term high-quality survival.

Methods

Participants

Volunteers will recruit from patients under 18 year-olds who are diagnosed monogenic immunodeficiency T1DM in Children's Hospital of Fudan University. Inclusion Criteria include: 1. Meet the diagnostic criteria of type 1 diabetes mellitus: clinical manifestations of typical diabetes mellitus include polyphagia, polyuria, weight loss, or diabetic ketoacidosis, confirmed by blood sugar level, islet function and autoimmune antibody; 2. Existence of extrapancreatic organ damage: (1) inflammatory bowel disease, (2) impairment of renal function, (3) repeated infection of mouth, skin, anus or whole body, (4) immune hepatitis, (5) persistent chronic immune iridocyclitis, (6) immune adrenalinitis leading to adrenocortical dysfunction, (7) pituitary inflammation

leading to hypophysis, (8) rheumatoid disease, (9) immune vasculitis, (10) systemic lupus erythematosus, (11) other organs besides thyroid function damage. Suffering from one or more of above diseases. Recurrence after receiving regular clinical treatment, including symptomatic treatment of organ protective drugs. 3. Gene mutation was found according to gene diagnosis: gene mutation was found by gene sequencing. Literature searches at home and abroad confirmed that the defect of the gene resulted in autoimmune or immune dysfunction, resulting in multiple organ dysfunction and poor prognosis. Exclusion Criteria include: mature and effective treatment methods are available; HIV, HBV and HCV were positive; at the active period of infection; at the active stage of malignant tumors; combination of other fatal diseases; and existence of mental and psychological diseases.

Interventions

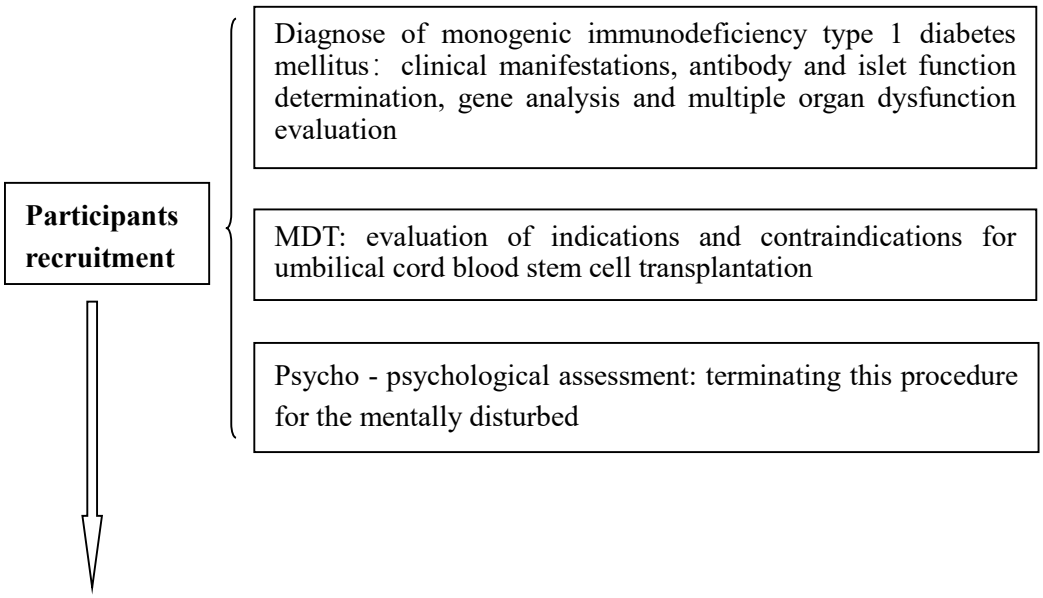
The interventions will be divided into two stages. The first stage is the transplantation of umbilical cord blood stem cells: (1) T1DM children with monogenic immunodeficiency confirmed by islet function, autoantibody and gene analysis; (2) high resolution typing of histocompatibility antigens in children; (3) matching of stem cells in the national umbilical cord blood bank; (4) admitting children to the transplantation cabin to obtain matching umbilical cord blood stem cells after immune clearance; (5) after successful transplantation, they were removed from the transplantation cabin and entered the follow-up stage of outpatient clinic.

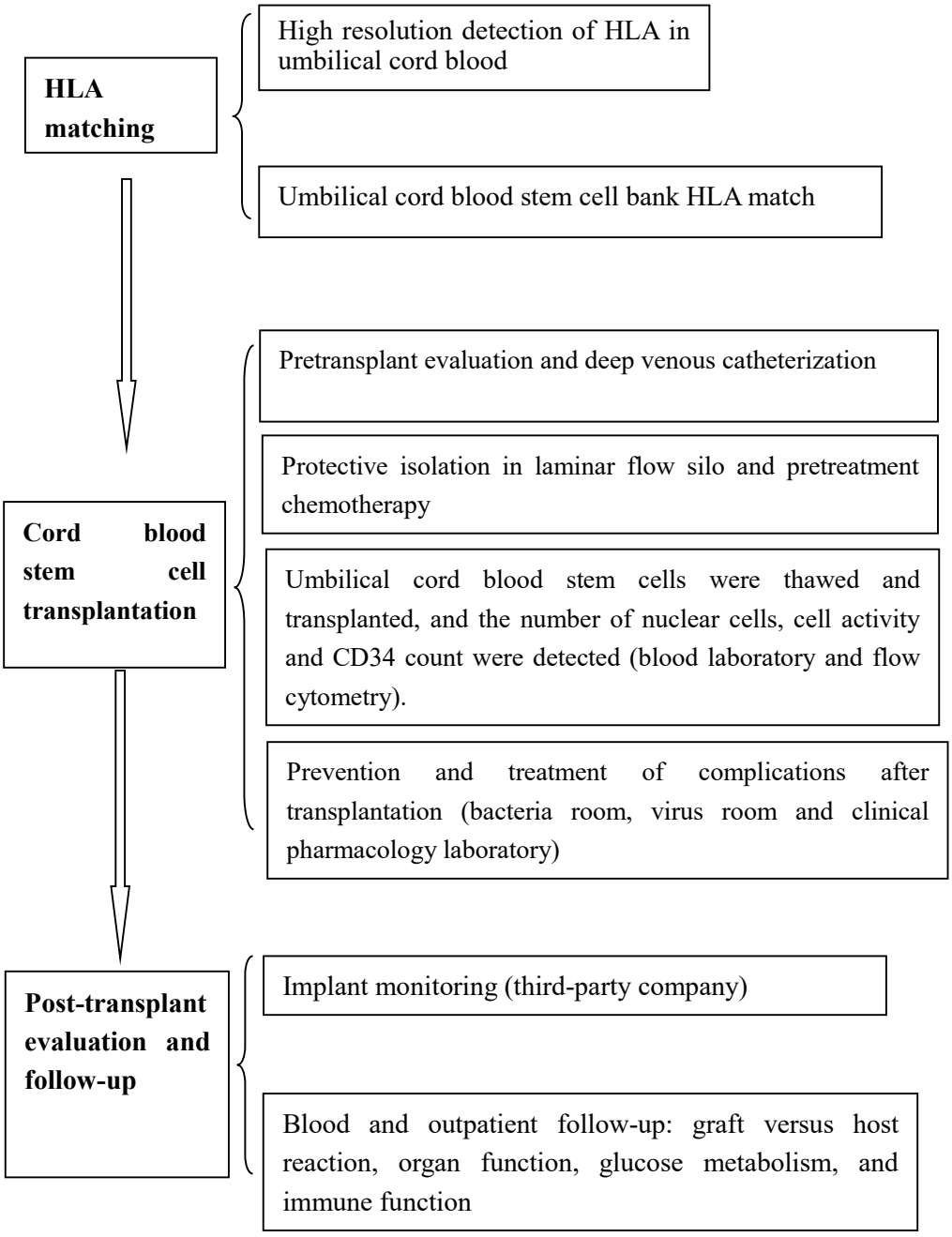
The second stage is islet cell transplantation. After successful umbilical cord blood transplantation and stable immune function, the children begin islet cell transplantation:

(1) obtaining the pancreas of donors; (2) extracting pancreatic cells; (3) purifying islet cells to obtain high purity and high activity islet cells; (4) using immunosuppressive agent Basiliximab (Simulect) 6 hours before operation and injecting purified islet through portal vein puncture; (5) Tacrolimus combined with mycophenolate mofetil (Mycophenolate) will be used after operation, and blood concentrations will be measured. The amount of immunosuppressive drugs will be gradually reduced. Finally, gradually reduce insulin according to blood glucose. We will follow up the glucose metabolism, immunity and growth of patients for in long term.

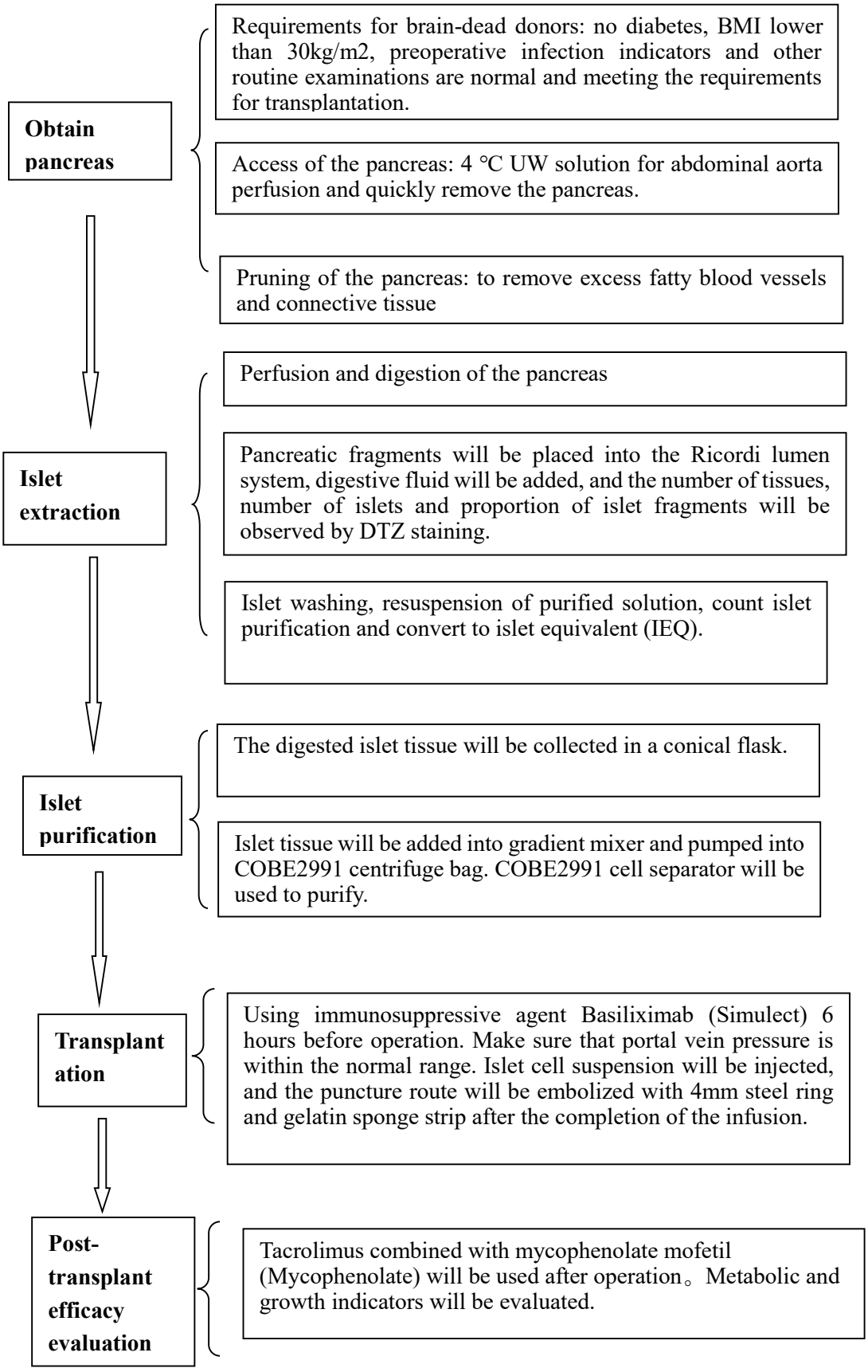
Flow chart to illustrate the study

Stage1: Cord blood stem cell transplantation:




HLA matching
High resolution detection of HLA in umbilical cord blood
Umbilical cord blood stem cell bank HLA match
Cord blood stem cell transplantation
Pretransplant evaluation and deep venous catheterization
Protective isolation in laminar flow silo and pretreatment chemotherapy
Umbilical cord blood stem cells were thawed and transplanted, and the number of nuclear cells, cell activity and CD34 count were detected (blood laboratory and flow cytometry).
Prevention and treatment of complications after transplantation (bacteria room, virus room and clinical pharmacology laboratory)
Post-transplant evaluation and follow-up
Implant monitoring (third-party company)
Blood and outpatient follow-up: graft versus host reaction, organ function, glucose metabolism, and immune function

Stage 2: Islet cell transplantation



Adverse reactions:

1. Pretreatment related to chemotherapy or radiotherapy: nausea, vomiting, diarrhea, hematuria, alopecia, oral ulcer, bone marrow suppression, liver and kidney damage, infection, bleeding, skin damage, etc.

2. Graft-versus-host reaction (GVHD).

3. Opportunistic infection of immunodeficiency.

4. Infertility.

5. Occurrence of other tumors.

6. Allergic reactions caused by anesthetics, contrast agents and therapeutic drugs.

7. Islet injection leads to vascular embolism and abnormal liver function.

8. If puncture is difficult, open portal vein injection may be used instead.

9. Immunosuppressive agents cause kidney and other toxic and side effects.

10. Portal vein puncture may lead to intrahepatic and extrahepatic vascular hemorrhage.

11. Opportunistic infections (viral fungi, etc.) occur after transplantation.

12. Cardiovascular events, graft loss, abnormal coagulation, pulmonary embolism and other cardiovascular events

Risk assessment and contingency plans

1. Adverse reactions: regular assessment of organ function, monitoring of blood, preventive use of anti-infective drugs, use of immunosuppressive agents to prevent GVHD, bedside call system, ECG monitoring, suction devices and oxygen. Severe cases can be transferred to Laminar Flow Ward, Department of Critical Care Medicine,

our hospital.

2. Contamination of umbilical cord blood stem cells: to ensure that the source of umbilical cord blood stem cells is legitimate, and to establish a registration system for the source of umbilical cord blood stem cells. Umbilical cord blood stem cells for transplantation are collected by medical institutions that meet the technical management standards of umbilical cord blood stem cell collection. Strictly abide by the relevant technical specifications and guidelines for diagnosis and treatment of umbilical cord blood stem cell transplantation. Several suitable umbilical cord blood donors were retrieved for reserve before transplantation.

3. Implantation failure: monitoring blood picture after implantation and regular chimerism examination. Before transplantation, HLA matching searches multiple suitable umbilical cord blood donors for consideration of secondary transplantation after implantation failure.

4. The most serious complications after islet transplantation are hemorrhage and thrombosis caused by liver and portal vein puncture. Islet transplantation was given heparin to prevent thrombosis, and anticoagulant therapy was continued after operation. After operation, a surgical hemostatic gel / steel ring was used to close the needle channel outside the portal vein.

Quality control measures

1. Strictly grasp the indications of transplantation of umbilical cord blood stem cells and islets. According to the patient's condition, the treatment options and other factors,

we can make a comprehensive judgment and treat the disease scientifically and rationally.

2. The source of umbilical cord blood stem cells is legitimate, and the registration system of the source of umbilical cord blood stem cells is established to ensure that the source of umbilical cord blood stem cells can be traced. Umbilical cord blood stem cell transplantation is not allowed to seek unfair benefits, nor is it allowed to divulge the information of umbilical cord blood stem cell donors.

3. Umbilical cord blood stem cells for transplantation are collected by medical institutions that meet the technical management criteria of umbilical cord blood stem cell collection. The transplanted islets were collected by medical institutions in accordance with the criteria for islet isolation, purification and evaluation.

4. Inform and sign informed consent before transplantation of umbilical cord blood stem cells and islets.

5. Strictly abide by the relevant technical specifications and guidelines for diagnosis and treatment of umbilical cord blood stem cells and islet transplantation.

6. Establish a follow-up system after transplantation of hematopoietic stem cells and islets.

7. Strictly implement the national price policy and charge fees according to regulations.