Cyclophosphamide in the Treatment of Panniculitis Associated Acquired Lipodystrophy Syndrome With Type 1 Diabetes

2019-04-09

Background

Lipodystrophy Syndrome is a kind of rare metabolic diseases with a global incidence of about 3.07/1,000,000. Patients with lipodystrophy syndrome often have severe metabolic syndrome in childhood, which affects the life span and quality of life of patients. However, there is no effective treatment for curing this disease at home and abroad.

Panniculitis associated acquired lipodystrophy syndrome leads to severe insulin resistance

Lipodystrophy syndrome is a class of rare metabolic diseases in which there is generalized or localized subcutaneous fat deficiency without the absence of nutrients or catabolism. Patients with lipodystrophy syndrome are clinically characterized by enormous appetite and severe metabolic disorders, including hyperinsulinemia, hyperlipidemia, nonalcoholic fatty liver and cirrhosis, and high metabolic rate.

Insulin resistance is the major feature of lipodystrophy syndrome. Low leptin levels due to loss of subcutaneous fat, increased expression of tumor necrosis factor 1 in immature adipose tissue, increased levels of free fatty acids in the blood, and deposition of fat in the liver and muscle lead to severe insulin resistance and diabetes in patients with lipodystrophy syndrome. One study suggested that approximately 70% of patients with acquired systemic dystrophy syndrome develop diabetes during the course of the disease. Due to early onset, long course of disease, and difficulty in correcting metabolic disorders, these patients have early cardiovascular events, especially the high risk of developing atherosclerotic cardiovascular disease, which seriously affects the

life and quality of life of patients. There is currently no effective method for curing lipodystrophy syndrome. Patients can only follow blood glucose, blood lipids and related complications regularly, and manage blood lipids and blood glucose and increase insulin sensitivity through lipid-lowering drugs, metformin, and thiazolidinediones as those with hyperlipidemia and diabetes.

Autoimmune factors may be the common cause of panniculitis associated acquired lipodystrophy syndrome and type 1 diabetes

Acquired lipodystrophy syndrome often onsets in childhood or adulthood and has a complex cause. In addition to HIV or drugs associated acquired fatty dystrophy syndrome, autoimmune factor is considered to be the leading cause of acquired lipodystrophy syndrome. Some patients with acquired lipodystrophy syndrome have positive autoantibodies, and about 67% of patients with acquired lipodystrophy syndrome have autoimmune diseases such as Hashimoto's thyroiditis, rheumatoid arthritis, and hemolytic anemia. More than 1,141 children have been reported to have autoimmune diseases in patients with acquired lipodystrophy syndrome.

Among the patients with acquired lipodystrophy syndrome, a quarter of patients suffer from subcutaneous panniculitis, known as panniculitis associated acquired lipodystrophy syndrome. Inflammatory infiltration of subcutaneous adipose tissue is also a strong evidence of autoimmune response.

Type 1 diabetes is a type of diabetes characterized by a lack of insulin secretion. Islet beta cells are gradually destroyed by chronic autoimmune processes and eventually lead to complete insulin deficiency in a short period of time. Islet autoantibodies such as

ICA, IAA, GADA, and IA-2A can be detected in patients with type 1 diabetes.

Patients with lipodystrophy syndrome often have type 2 diabetes due to insulin resistance, but cases with type 1 diabetes are rare. Three cases of acquired lipodystrophy combined with type 1 diabetes have been reported worldwide. Since the autoimmune response plays an important role in both of the pathogenesis of panniculitis associated acquired lipodystrophy syndrome and type 1 diabetes, we believe that autoimmune factors may be the common cause of these two diseases.

Patients with panniculitis associated acquired lipodystrophy syndrome and type 1 diabetes have difficulty in managing glucose metabolism due to suffering from insulin deficiency and insulin resistance at the same time

Patients with acquired lipodystrophy syndrome combined with type 1 diabetes have severe insulin resistance and absolute insulin deficiency, thus they need to rely on insulin several times of that of other common type 1 diabetes patients to control blood sugar, but often still cannot get satisfactory results. What's more, insulin sensitizing drugs such as metformin and thiazolidinediones have limited effects in these patients.

The recombinant human leptin analog, Metreleptin, is currently the only drug that can specifically address the metabolic problems of patients with lipodystrophy syndrome. Foreign clinical trials have confirmed that Metreleptin can inhibit appetite, lower blood lipid levels, improve glucose metabolism and alleviate nonalcoholic fatty liver disease in patients with lipodystrophy syndrome. In patients with acquired lipodystrophy syndrome and type 1 diabetes, Metreleptin reduces insulin resistance and reduces insulin use in some patients. But Metreleptin is not yet available in China and the cost

is high. At the same time, about one-third of patients experienced different degrees of side effects after receiving Metreleptin injection, including headache, hypoglycemia, allergic reactions at the injection site, hair loss, fatigue, and T-cell lymphoma. What's more, one study found that more than 80% of patients treated with Metreleptin developed leptin antibodies, which may lead to insensitivity to leptin, resulting in reduced efficacy and even treatment failure. This raises questions about the long-term efficacy of Metreleptin.

Cytotoxic drugs may improve the glucose metabolism of patients with acquired lipodystrophy syndrome and type 1 diabetes, and may even achieve clinical remission

Cyclophosphamide is a commonly used immunosuppressant in patients with autoimmune diseases. It is mature in pediatric use and has controllable adverse reactions. It is one of the first choices for children with nephrotic syndrome, systemic lupus erythematosus and rheumatoid arthritis. It can also be used in patients with autoimmune-associated panniculitis who cannot tolerate glucocorticoids. In view of the fact that autoimmune factors may be the common cause of panniculitis associated acquired lipodystrophy syndrome and type 1 diabetes, immunomodulatory therapy may improve the insulin resistance of these patients from the etiology, reduce the amount of insulin to use, and even achieves the effect of preventing disease progression and clinical cure.

Objectives

To improve the insulin resistance, reduce the daily dosage of insulin and control the blood glucose level of patients with panniculitis associated acquired lipodystrophy syndrome, we plan to use cyclophosphamide to inhibit the immune response, prevent and alleviate the progression of panniculitis and acquired lipodystrophy syndrome, and improves insulin resistance caused by subcutaneous fat deficiency.

Methods

Participants

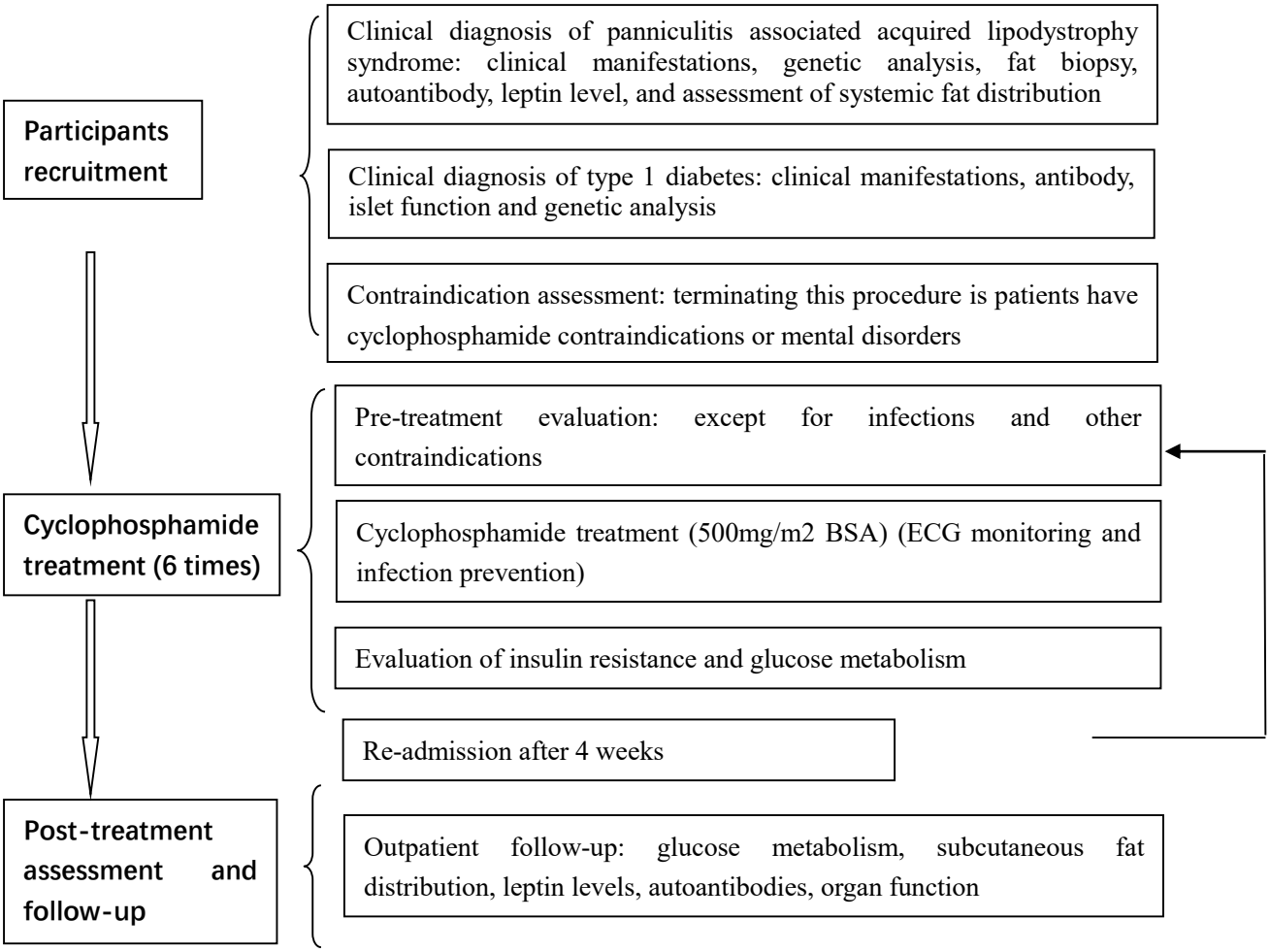
Volunteers will recruit from patients who are diagnosed panniculitis associated acquired lipodystrophy syndrome and T1DM in Children's Hospital of Fudan University. Inclusion Criteria include: 1. Meet the diagnostic criteria of type 1 diabetes mellitus: clinical manifestations of typical diabetes mellitus include polyphagia, polyuria, weight loss, or diabetic ketoacidosis, confirmed by blood sugar level, islet function and autoimmune antibody; 2. Meet the diagnostic criteria for panniculitis: fat biopsy suggests inflammatory infiltration. 3. Meet the diagnostic criteria for acquired lipodystrophy syndrome: childhood onset, clinically no nutritional deficiency or catabolism, systemic or partial subcutaneous fat reduction, genetic testing to exclude congenital lipodystrophy syndrome; low leptin level and autoantibodies can aid in diagnosis.

Interventions

The patient meet the diagnosis of panniculitis associated acquired lipodystrophy syndrome and T1DM and was rigorously evaluated and discussed. He had the

indication for the application of cyclophosphamide and no contraindications, and informed and signed the informed consent form. The patient will receive 6 cycles of cyclophosphamide treatment. Cyclophosphamide was intravenously instilled (500mg mg/m2 of BSA). Each treatment interval is 4 weeks. Patients will be carefully assessed for contraindications before each treatment. And the daily insulin usage, fast blood glucose level, serum C-peptide level, HbA1c and abdominal subcutaneous fat thickness will be measured and recorded after each treatment. When finish the total 6 treatment cycles, patients will receive long-term follow-up for 3 years.

Flow chart to illustrate the study



Adverse reactions:

1. Infection: There may be infections of various organs, including bacteria, fungi, viruses and other pathogens, especially lung infections and intracranial infections, which can be life-threatening in severe cases.

2. Important organ damage: There may be damage to important organs, such as heart, liver, kidney, lungs, etc. Some damage may not be fully restored even if the drug is stopped.

3. Myelosuppression: anemia which is difficult to correct; thrombocytopenia, bleeding such as mucous membrane bleeding, digestive tract, urinary tract bleeding, intracranial hemorrhage and other parts of the bleeding; granulocyte reduction, various serious infections, septicemia, shock, etc.

4. Musculoskeletal and nervous system damage: cause muscle weakness, numbness of the limbs, headache, blurred vision, etc; may induce epilepsy. Osteoporosis can cause femoral head necrosis and fracture deformation in severe cases.

5. Gastrointestinal reactions.

6. Phlebitis.

7. Reproductive system toxicity.

8. Drug allergies, anaphylactic shock, etc.

9. Other unforeseen, unpredictable and precautionary situations: Long-term use increases the risk of developing a tumor.

10. There are other unpredictable risks and adverse reactions and consequences that may jeopardize the life of the child.

Risk assessment and contingency plans

1. Adverse reactions: Regular assessment of organ function, exclusion of potential infections before each dose, bedside equipped call system, ECG monitoring, suction device and oxygen. Severe cases can be transferred to the laminar flow ward of the Department of Critical Care Medicine.

2. Ineffective in the treatment of cyclophosphamide: closely monitor blood sugar, actively adjust the insulin dose, and rationally use oral hypoglycemic drugs to correct the children's metabolic disorders.

3. Primary disease-related complications: Type 1 diabetes patients may have acute complications such as ketoacidosis and chronic complications such as retinopathy and peripheral neuropathy; patients with lipodystrophy syndrome often have hyperlipidemia, polycystic ovary syndrome, non-alcoholic fatty liver and so on. Children enrolled will receive regular assessments to screen for the occurrence of related complications and receive appropriate treatment.

Quality control measures

1. Strictly grasp the indications of cyclophosphamide. 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. Perform notification and sign informed consent before the implementation of cyclophosphamide treatment.

3. Strict screening for contraindications prior to treatment with cyclophosphamide.

4. Establish a follow-up system after cyclophosphamide treatment.

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