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Case Report .

One Year Therapy with Cyclosporine A is Useful in Prevention of Early Autoimmune Transformations in Predisposed Patients for Type I Diabetes Mellitus

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ABSTRACT

Type 1 diabetes (T1D) is a chronic autoimmune disorder characterized by specific immune destruction of the insulin-producing pancreatic β-cells. The loss of β cells involves both genetic and ill-defined environmental factors. The highest risk HLA-DR3/4 DQ8 genotype has been shown to be highly associated with β-cell autoimmunity and benign insulinitis. Subsequently; catalysts viz. viruses transform predisposed subjects into overt diabetics. Such autoimmunity is herald by autoantibodies and subsequently low C-peptide production. Hence, there is no ideal autoimmune therapy for T1D since patients are genetically predisposed. Previous autoimmune measures to suppress early transformations were crippled by long-term complications of medications. In our case report; we limited the use of Cyclosporine A to 1 year in a patient and it was cost effective.

Keywords: Autoantibodies, Diabetes, Cyclosporine A.

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INTRODUCTION

Type 1 diabetes (T1D) is a chronic autoimmune disorder characterized by specific immune destruction of the insulin-producing pancreatic β-cells.[1] It comprises the majority of cases of diabetes seen in childhood and approximately, 5-10% of all cases of diabetes mellitus in the USA. The incidence of T1D is rapidly rising in children, with a predicted 70% increase in incidence over the next 15 years in Europe. Furthermore, the age of onset is also decreasing, with a predicted doubling of cases in children under the age of 5 years during the same period.[2] Despite refined treatment with insulin therapy, long-term complications, including nephropathy, retinopathy, neuropathy, and cardiovascular disease, can appear.[3] Prevention of the development of T1D is the ideal management of this disorder. In this case report; we describe our experience with Cyclosporine A (Cy A) in this context.

CASE REPORT

A 16 year-old boy was admitted, to our center, with malaise and fainting attacks in the past month. Past history was significant for gastroenteritis and pancreatitis 9 months ago. That illness was self-limited within few days. On his initial physical examination, the patient was conscious, oriented X3 and without distress of shortness of breath or pain. Blood pressure was 100/60 mm Hg and with postural hypotension to 80/50 mm Hg. He was afebrile with a body weight of 77 kg. He did not have lymphadenopathy, goiter, jugular venous distension or oedema. Systemic examination did not show abnormality. Laboratory investigations showed normal peripheral leukocytic and platelets counts. Hemoglobin was normal with normal MCV. Serum sugar was 22 mmol/L. Serum urea and creatinine were elevated at 12 mmol/L and 140 umol/L, respectively. Serum electrolytes and liver functions were normal except for bicarbonate at 8 mmol/L. Serum amylase and lipase were normal. Serum cholesterol was 6 mmol/L. TSH was normal. Urine routine and microscopy showed 4 (+) glucose and ketones. C-peptide insulin was 150 pmol/L with normal level 160-1160 pmol/L. Anti-insulin antibodies were 24 IU/ml with normal levels < 10. Anti-islet cell antibody was positive. Chest x-ray and ECG were normal. Abdominal and pelvic ultrasound was normal. Chest x-ray and ECG were normal. His condition improved after rehydration, correction of electrolytes

deficiencies and control of hyperglycemia with insulin drip. Subsequently, he was discharged with controlled blood sugar on Lantos 48 units pm and Novorapid 8, 14 and 6 units before respective meals. Cy A was started at a dose of 100 mg twice daily in an attempt to treat his underlying T-cell activation. Subsequently, his requirement for insulin had decreased with time and ultimately it was discontinued 2 months later. All his antibodies disappeared and his C-peptide insulin had increased to 1356 pmol/L. After 1 year of Cy A therapy, his blood sugar remained normal, the autoantibodies were not detected and his C-peptide insulin remained normal at 1115 pmol/L. Hence, Cy A was discontinued. One year later his blood sugar and C-peptide insulin remained normal and his autoantibodies remained negative.

DISCUSSION

The loss of β cell involve both genetic and ill-defined environmental factors. A strong genetic association with specific human leukocyte antigen (HLA) haplotypes, coupled with several variants of genes expressed by β-cells, T cells, and other immune effectors underscore the complexity of the autoimmune response in T1D.[4] It has been reported that approximately 50% of the genetic risk for T1DM can be attributed to the HLA region. The highest risk HLA-DR3/4 DQ8 genotype has been shown to be highly associated with β-cell autoimmunity. Beta-cell autoimmunity is typically viewed as a chronic inflammatory response characterized by progressive infiltration of the pancreatic islets with various immune effectors.[5] In the nonobese diabetic mouse, a spontaneous model of T1D, islet infiltration is initiated at an early age by macrophages and dendritic cells, $CD4^+$ and $CD8^+$ T cells, and B cells. This insulinitis initially exhibits benign properties with little effect on β cell viability or function. However, at a late preclinical stage, an ill-defined qualitative change occurs within the islet infiltrate, which promotes efficient β cell destruction leading to the onset of overt diabetes.[6] The catalysts for such transformation of predisposed subjects are ill defined yet include viruses viz. Coxsackie B4.[7] Pathogenic β cell-specific $CD4^+$ and $CD8^+$ Teff in NOD and human T1D typically exhibit a type 1 or T helper 1 phenotype marked by IFNγ production.[8] The first antibodies described in association with the development of T1DM were islet cell autoantibodies (ICA). Subsequently, antibodies to insulin, glutamic acid decarboxylase (GAA or GAD) and protein tyrosine phosphatase (IA2 or ICA512) have all been defined.[2] Studies have shown that these bodies are the most intense single marker for identifying persons with increased risk for diabetes development.[9] Our patient had clinical response to Cy A therapy associated with suppression of autoantibody production which indicates its efficacy in prevention of D1T. Three months later, the dose of Cy A was reduced to 50 mg X2 without clinical relapse, decrease in C-peptide level and increase of autoantibodies. The latter dose, with its relatively low serum level, has been shown to be safe on the long run.[10] The goal of an immunotherapy is threefold: (1) selective suppression of an ongoing autoimmunity, (2) reestablishment of long-term self-tolerance, and (3) preservation of acquired immunity. Multiple immunotherapeutic agents have been tried to prevent T1D viz. Mycophenolate mofetil, Rituximab, Cytotoxic T-lymphocyte-associated protein 4 immunoglobulins, Anti-TNF agents, Anti-interleukin-1 drugs, Anti-interleukin-1β, Anti-CD3 agents an specific immunomodulative strategies for Foxp3+ regulatory (Treg) cells.[11]

Those immunosuppressive agents were declared ineffective in treatment of T1D since they did not produce long-term self-tolerance in such genetically predisposed patients. Hence; the most ideal approach is early prevention of autoimmune triggered transformations yet drug-therapy can be limited to only 1 year as in our patients to avoid the long-term side effect of interstitial fibrosis. In conclusion; 1 year therapy with Cy A is a cost-effective measure in prevention of transformations in clinical diabetes if started early.

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