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Two Years of Modified Protocol with Cyclosporin A for Treatment of Acute Insulin Resistance Induced by Anti-Glutamic Acid Decarboxylase (GAD) Antibodies in Obese Type II Diabetics

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Abstract

Background: Diabetes mellitus (DM) is a disease characterized by hyperglycemia due to (a) insulin-insufficiency (type I DM), or (b) impaired glucose cell-entry (insulin resistance) due to the downregulation of insulin cell receptors (type II DM). Type I DM usually presents with florid manifestations contrary to a slowly-progressive type II. **Patients and methods**: Over the past 10 years, we encountered 9 obese patients with controlled insulin-requiring type II DM for years, at a dose of 62 ± 5 units/day, who developed sudden and severe insulin resistance (IR) that required 210 ± 25 units daily. All patients had very high levels of anti-Glutamic Acid Decarboxylase (GAD) antibodies. Despite a lack of previous testing for anti-GAD antibodies, they were treated, with Cyclosporin A (Cy), as an autoimmune disorder superimposed on their type II MD. Initially all patients were treated with 100 mg, of Cy, twice daily aiming at an initial trough level of 100 - 150 ng/ml. Three months later, the dose was reduced to 50 mg twice daily for a total of 2 years. **Results**: Amelioration of IR was achieved by 1 month with a reduction of daily insulin requirement to 123 ± 16 units that further decreased to 76 ± 11 by the end of the 3rd month. Such improvement persisted for 2 years and >1 year after Cy discontinuation. Moreover, a decline in insulin requirements was associated with a parallel decrease in anti-GAD antibody levels and an increase in C-peptide insulin without kidney disease. **Conclusion**: Anti-GAD antibodies can induce acute IR in type II DM, and this phenomenon can be treated safely and effectively with Cy.

Keywords

Anti-GAD Antibodies, C-Peptide, Cyclosporin A, Diabetes Mellitus, Hyperglycemia, Insulin, Resistance, Therapy

1. Introduction

Diabetes mellitus is a disease characterized by hyperglycemia due to (a) insulin-insufficiency (type I DM), or (b) impaired glucose cell-entry due to the downregulation of insulin cell-receptors (type II DM). Both can be induced by different genetic mutations, infections and autoimmunity [1]. Type 1 DM results from the autoimmune destruction of the pancreatic beta-cells of islets of Langerhans (BcL), in genetically susceptible individuals, in whom the autoimmune process is triggered by one or more environmental factors [2]. Induction of such autoimmune disease is usually florid and is associated with high levels of anti-islet cell antibodies especially anti-glutamic acid decarboxylase antibodies (anti-GAD antibodies). On the other hand, type II DM is a slow and chronic disease induced, in genetically susceptible patients, by intestinal derived apoB-48 in excessive visceral adiposity (lipotoxicity) that is mediated by proinflammatory cytokines viz. tumor necrosis factor-alpha and interleukins 1 & 6 [3]. Uncontrolled type II DM is commonly encountered in stress, infections, drugs, progressive obesity, and lack of drug and/or dietary compliance [4]. In the present study, we describe a new phenomenon of severe and acute hyperglycemia with insulin resistance (IR) in patients with previously stable type II DM that was associated with high levels of anti-GAD antibodies indicating superimposed type I disease.

2. Patients and Methods

Over the past 10 years, patients were included in the study if they had (a) stable obesity, (b) type II DM, (c) stable insulin requirements for years, (b) adequate dietary compliance, (e) no history of significant kidney disease that was confirmed by e-GFR > 60 ml/minute, lack of proteinuria and normal kidney ultrasound, (c) no history of previous liver disease which was confirmed by normal liver enzymes and abdominal ultrasound as well normal cardiac function with normal cardiac enzymes, chest x-ray, and echocardiogram, (d) no history of disorders requiring drugs interfering with Cy-blood levels viz. epilepsy, hypertension, and chronic infections, (e) negative history, clinical examination, radiological scans as well as laboratory and serological tests for autoimmune diseases, infections, malignancy and drugs-side effect, and (f) adequate follow up for >3 years.

2.1. Study Design

Initially all patients were stabilized with higher dosages of long and short acting insulin. At the same time, Cy was started at a dose of 100 mg twice daily aiming at an initial trough level of 100 - 150 ng/ml for 3 months (induction phase). After

the induction phase, Cy-dose was reduced to 50 mg twice daily till the end of the study at 2 years (maintenance phase). Subsequently, patients were followed up for a minimum of 1 year.

2.2. Periodic Assessment

Patients were seen on a monthly basis for the first 3 months, then every 2 months. In those visits, patients were assessed clinically for the severity and complications of their DM as well as the side effects of therapy. During those visits, laboratory investigations were done and included complete blood count as well as serum estimates of sugar, renal, liver function tests, lipid profiles and urine routine. Twenty-four-hour urine collections for daily protein excretion (Pr) and creatinine clearance (CrCl) were done at times 0, 3 months, 6 months, 12 months, 24 months and 36 months then every 6 months subsequently.

2.3. Statistical Analysis

SPSS statistical package version 25 was used for data entry and processing. Since age, insulin requirements, anti-GAD antibodies, C-peptide insulin as well as duration of previous DM, IR, and follow up were normally distributed, they were expressed as mean ± SD. Comparison of the individual changes in daily insulin requirements, anti-GAD antibody titers and C-peptide levels at different times (0, 3 months, 2 years, 3 years) was done using t-test and the overall changes with ANOVA for repeated measures. The p-value ≤ 0.05 was used as the cut-off level for significance.

3. Results

A total of 9 patients fulfilled the study inclusion-criteria. The patient's demographic characteristics and response to Cy-therapy are summarized in Table 1. All patients were adults (age: 44 ± 6 years) of whom 6 were females. All were obese with a BMI of 36 ± 2 kg/m^2. All patients had stable type II DM for 85 ± 7 months and their IR was confirmed for 11 ± 3 months. Their follow-up was 82 ± 17 months.

3.1. Response to Therapy

As shown in Table 1, amelioration of IR was achieved by 1 month with a significant reduction in insulin requirement to 123 ± 16 that further decreased to 76 ± 11 by the end of the 3rd month ($p < 0.000001$). Such improvement persisted for 2 years and >1 year after Cy discontinuation. Moreover, a decline in insulin requirements was associated with a parallel significant decrease in anti-GAD antibody levels and an increase in C-peptide insulin. Such improvement persisted for >1 year, after Cy-discontinuation.

3.2. Side Effects of Therapy

Cy therapy led to mild darkening of skin color and hirsutism in most patients as

well as mild gum hyperplasia in 2 patients. They were tolerable and decreased significantly after dose-decrement. None of the patients manifested decreased creatinine clearance and/or increased proteinuria.

Table 1. Demographical data and response to Cyclosporin A in type II diabetics with acute IR due to anti-GAD antibodies.

Patients' characteristics:				
Total	9 patients			
Demographical data:				
Gender (F/M)	6/3			
Mean age (years)	44 ± 6			
BMI (kg/m^2)	36 ± 2			
Duration of type II DM (months)	85 ± 7			
Duration of insulin resistance (weeks)	11 ± 3			
Duration of follow up (months)	82 ± 17			
Cyclosporin A therapy:				
	Daily dose	Response*		
		Insulin requirements (units/day)	Anti-GAD AB (IU/ml)	C-peptide insulin (ng/ml)
Time 2 months:		62 ± 15	NA	NA
Time 0:	100 mg X2	210 ± 25	98 ± 3	5 ± 1
Time 1 month:	100 mg X2	123 ± 16	32 ± 6	6 ± 1
Time 3 months:	100 mg X2	76 ± 11	19 ± 1	7 ± 1
Time 3 months - 2 years:	50 mg X2			
Time 2 years:	50 mg X2	72 ± 9	15 ± 1	8 ± 1
Time 2 - 3 years:	None			
Time 3 years:	None	71 ± 7	14 ± 1	8 ± 1

Normal range: C-peptide insulin: 1.1 - 4.4 ng/ml, anti-GAD AB: <17 IU/ml. Abbreviations: IR: insulin resistance, DM: diabetes mellitus, GAD: anti-Glutamic acid decarboxylase antibodies. BMI: body mass index, NA: not available. * Significance (p): (a) 0.00001 in the 3 parameters at all time tested (−2, 0, 1, 3 months and 2, 3 years). (b) between 2 and 3 years: not significant.

4. Discussion

Normally, elevated blood glucose from basal liver production and dietary-addition induces insulin release from BcL. Insulin facilitates glucose cell entry via its cell receptors in muscles and the liver. Glucose cell-entry is essential for both cellular energy production (via Kreps cycle) and storage (as glycogen) [5]. Impairment leads to hyperglycemia (DM) which is the precursor of serious metabolic complications and progressive ischemic heart disease and strokes [6]. Such a disorder is common worldwide, and in 2021, nearly 537 million individuals will be living with diabetes, making up 10.5% of the global population, resulting in global healthcare expenses amounting to $966 billion [7]. Type II DM makes up over 90% of DM cases [8]. Management of these patients includes early diagnosis,

lifestyle modifications (diet, weight loss, exercise and smoking cessation), oral drug-therapy and insulin. Such cohesive health strategies are commonly punctured with uncontrolled hyperglycemia especially due to a lack of compliance in this chronic disease [4]. In our study, we report another underestimated disorder in this patient population which is a superimposed autoimmunity similar to type I DM in type II patients. Derangement in diabetic control was associated with severe IR (insulin requirements at 200 units/day) and diagnosis was established with (a) high anti-GAD antibodies and (b) relatively lower C-peptide level from autoimmune destruction of BcL. Such a phenomenon is not seen in type II DM yet akin to insulin-requiring patients with DM viz. type I DM and Latent autoimmune diabetes in adults (LADA) [9]. Our finding is worrisome since misdiagnosis and lack of immunotherapy can lead to progressive increment in insulin therapy with its inherent risk of drug-cost, disease complications, accelerated obesity as well as insulin-associated atherosclerosis [10]. Previous studies have shown that GAD65 antibody is one of the strongest autoantibodies involved in BCL autoimmunity in genetically susceptible individuals and is observed in >80% of type I DM patients at diagnosis [11]. It inhibits the formation of gamma-aminobutyric acid (GABA) which is a neurotransmitter stored in membrane cytoplasmic microvesicles in BcL that releases insulin [12]. Type I DM is an autoimmune disease with a genetic predisposition that responds to external triggers by activation of $CD8^+$ T that activates B cells leading to autoimmune escalating-antibodies (anti-GAD antibodies) and destructive cytokines [13]. Such autoimmune flare/s can precipitate and enhance type I DM and LADA as well as induce type B IR in type II DM as seen in our study. Previous autoimmune treatments included repeated courses of Rituximab, Cyclophosphamide, pulse Corticosteroids, Cyclosporin A, Azathioprine, intravenous immunoglobulins, and plasmapheresis. Such protocols had mixed success, high cost and were associated with multiple side effects [14]. In fact; Cy was the first immunotherapy used in type I DM to target T-cells. In a landmark study by Feutren *et al.* in 1986, treatment with cyclosporin resulted in complete or partial diabetic remission during a 3-month treatment course, but the disease relapsed when cyclosporine was stopped [15]. However, further treatment was considered unjustified for fear of lifelong immunosuppression and renal interstitial fibrosis [16]. In our modified Cy-therapy for such an autoimmune phenomenon, we elected to use a step-wise protocol of adequate therapeutic dose of Cyclosporin A only for 3 months (induction-phase) followed by subsequent lower maintenance dose for 2 years only. The latter was a short-maintenance phase with lower Cy-dosage to overcome previous historical concerns. Such protocol proved to be effective in lowering anti-GAD antibodies and insulin requirements as well as protecting of BcL insulin-reserve with an increase in C-peptide levels. Limitations of the study include: (a) a limited number of included patients with such an uncommon disorder in 2 tertiary hospitals and a lack of previous levels of anti-GAD antibodies and C-peptide insulin. However, the results indicated an impressive decline in IR that persisted for 1 year after drug-discontinuation and without side effects.

5. Conclusion

Anti-GAD antibodies can induce acute IR in type II DM, and such phenomenon can be treated safely and effectively with Cy.

Author's Contributions

Prof/ Kamel El-Reshaid conceived the study, participated in its design, and drafted the manuscript. Dr. Shaikha Al-Bader participated in the study design, follow-up of patients, data collection and tabulation of data.

Data Availability Statement

The data provided in the current review are available from the references.

Conflicts of Interest

All authors have read and approved the final version of the manuscript. The authors declare no conflicts of interest regarding the publication of this paper.

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