Onset of Type 1 Diabetes Mellitus During Pegylated-interferon Alfa and Ribavirin Therapy for Chronic Hepatitis C Virus Infection

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A 16-year-old female was treated with pegylated-interferon (PEG-IFN) alfa (α)-2b and ribavirin combination therapy for chronic hepatitis C virus (HCV) infection. She attained rapid virological response. She presented with diabetic ketoacidosis after 41 weeks of therapy. Anti-glutamic acid decarboxylase antibodies and islet cell antibodies were negative. Her fasting serum C-peptide level was <0.1 ng/mL, and the treatment course was completed. This case underlines the importance of periodic plasma glucose monitoring in patients during and after PEG-IFN and ribavirin therapy. (J CLIN EXP HEPATOL 2012;2:86–87)

Pegylated-interferon (PEG-IFN) alfa (α) in combination with ribavirin is the approved treatment for chronic hepatitis C virus (HCV) infection. Since the first report of interferon (IFN)-induced type 1 diabetes mellitus (DM) in 1992 by Fabris et al,¹ there have been numerous reports from all over the world. Interferon in combination with ribavirin induces type 1 diabetes in a much shorter period compared with plain IFN.² Interferon-induced diabetes has not been reported from India till date. Here we report PEG-IFN-induced type 1 DM in a 16-year-old, who was on treatment for chronic HCV infection with PEG-IFN 2b and ribavirin.

CASE REPORT

A 16-year-old female who had undergone treatment for Ewing's sarcoma with right cleidectomy and chemotherapy turned seropositive for HCV (genotype 1 infection) at the end of the chemotherapy. She had raised HCV-RNA and was started on combination therapy with ribavirin 800 mg orally daily and plain IFN- α -2b 3 MIU subcutaneously (SC) thrice weekly and completed 78 doses of the same. She did not respond to plain IFN and was switched over to PEG-IFN- α -2b 50 μ g SC weekly and ribavirin 800 mg orally daily combination therapy. There was no

history of diabetes or other autoimmune diseases in her family members. Her weight was 46 Kg and her body mass index (BMI) was 21.9 Kg/m². Complete blood count showed a total leukocyte count of 4900/mm³, hemoglobin of 10.8 g/dL, and platelet count of 289,000/mm³. Biochemical investigations revealed random blood sugar 106 mg/dL, normal serum bilirubin, albumin 4.7, serum glutamic-pyruvic transaminase (SGPT) 44 U/L, and normal thyroid functions. Ultrasound abdomen showed normal sized liver with coarse echotexture and normal portal vein. No varices were seen on endoscopy. She attained a rapid virological response. Except for mild anemia, a period of 40 weeks of the combination therapy was uneventful.

She presented with features of severe ketoacidosis following the 41st dose of PEG-IFN. She gave a history of polyuria, polydipsia, and weight loss for <2 weeks. She had a random blood sugar of 431 mg/dL, with severe metabolic acidosis and urine ketone positivity. Her ketoacidosis was managed with intravenous (i.v.) insulin infusion and fluid replacement. She was discharged on regular subcutaneous insulin. Anti-glutamic acid decarboxylase (anti-GAD) antibodies and islet cell antibodies (ICA) were negative and her fasting serum C-peptide level was <0.1 ng/mL. Based on the clinical presentation and low C-peptide level, she was diagnosed with type 1 DM.

While there have been case reports endorsing the cessation of the IFN therapy after the onset of diabetes, our patient had a low C-peptide level indicating that majority of the islet cells were destroyed by then. The risk of worsening of diabetes due to HCV-induced insulin resistance, in the absence of a sustained virological response,³ outweighed the risks of worsening of type 1 DM due to further beta cell destruction with continuation of IFN. Hence, PEG-IFN and ribavirin were continued. Her HCV-RNA load at the end of 48 weeks of treatment with PEG-IFN and ribavirin was below detectable limits. Her current requirement

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Abbreviations: BMI: body mass index; DM: diabetes mellitus; HCV: hepatitis C virus; HLA: human lymphocyte antigen; ICA: islet cell antibodies; MHC: major histocompatibility complex; PEG-IFN: pegylated-interferon; SC: subcutaneously; SGPT: serum glutamic-pyruvic transaminase
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of insulin is around 34 units/day of injection human Mixtard 30/70, and she has no evidence of thyroid dysfunction.

DISCUSSION

The combination therapy of PEG-IFN with ribavirin is the approved treatment of chronic HCV infection. Interferon- α through its immunomodulatory properties decreases the viral load.⁴ The immunomodulation is achieved through increasing the expression of both (major histocompatibility complex) MHC I and MHC II molecules on the surface of cells among other proposed mechanisms.⁵ Understandably, increase in expression of these molecules increases the chances of autoimmunity.⁶

Autoimmune thyroiditis⁷ is a well-known complication of IFN- α therapy. Other autoimmune phenomena reported include autoimmune hepatitis,⁸ autoimmune hemolytic anemia,⁹ autoimmune thrombocytopenic purpura,¹⁰ and systemic lupus erythematosus.¹¹ Interferon- α -induced type 1 DM is one of the less known complications. Interferon-induced DM is usually associated with the presence of antibodies, singular or multiple (ICA, anti-GAD antibody, islet autoantibodies, anti-insulinoma antigen-2 antibodies).² The antibodies are supposed to augment the T-cell-mediated response against the beta cells.¹² Increase in MHC II expression and the antibody-mediated potentiation of autoimmunity triggers the onset of type 1 DM in the individuals with a susceptible human lymphocyte antigen (HLA) genotype.

The incidence of type 1 DM in the population being treated with IFN for various conditions has been reported to be much higher than in the general population, the lowest rate of incidence being 10 times higher than in the general population.¹³ In a recently conducted study, the percentage of type 1 DM induced by IFN is about 1%, making it a significant cause of type 1 DM.²

This is the first case of IFN-induced DM to be reported from India and it stresses the importance of periodic blood glucose monitoring and identification of individuals at

high-risk for type 1 DM before the initiation of antiviral treatment with PEG-IFN.

CONFLICTS OF INTEREST

All authors have none to declare.

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