Peginterferon (PEG-IFN) Plus Ribavirin Combination Therapy, but neither Interferon nor PGE-IFN Alone, Induced Type 1 Diabetes in a Patient with Chronic Hepatitis C

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Abstract

Interferon (IFN) therapies, including IFN, peginterferon (PEG-IFN) and ribavirin (RBV) plus PEG-IFN combination, are widely used for patients with chronic hepatitis C. We encountered a patient with chronic hepatitis C in whom previous IFN or PEG-IFN alone had not induced type 1 diabetes (T1D), while the addition of RBV to PEG-IFN did induce T1D. The patient had HLA types conferring highly susceptibility to T1D. Thus, adding RBV to PEG-IFN may render chronic hepatitis C patients, with T1D-susceptible HLA types, more prone to developing T1D than IFN or PEG-IFN alone. To prevent T1D development, we recommend HLA typing prior to initiating RBV plus PEG-IFN administration.

Key words: human leukocyte antigen, anti-glutamate acid decarboxylase (GAD) antibody, anti-insulinoma-associated antigen (IA)-2 antibody, autoimmune disease

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Introduction

Interferon (IFN) therapies, including IFN, peginterferon (PEG-IFN) and ribavirin (RBV) plus PEG-IFN combination, are widely used for patients with chronic hepatitis C. Until recently, IFNα was the main option for treating chronic hepatitis C (1). Now, peginterferon (PEG-IFN, polyethylene glycol-binding IFN) combined with ribavirin (RBV), which augments IFN action, is a standard anti-viral therapy for chronic hepatitis C (2). However, IFN therapy can adversely impact the immune system and induce autoimmune diseases including type 1 diabetes (T1D) (3, 4). Not only IFN, but also PEG-IFN (5) and PEG-IFN plus RBV therapy (6, 7), can reportedly induce T1D. We encountered a patient with chronic hepatitis C in whom neither IFN nor PEG-IFN alone induced T1D, while RBV plus PEG-IFN did induce T1D with elevated anti-glutamate acid decarboxylase (GAD) and anti-insulinoma-associated antigen (IA)-2 antibodies. Herein, we emphasize the risk of T1D development with PEG-IFN plus RBV therapy.

Case Report

A woman was diagnosed as having chronic hepatitis C at the age of 53 and received IFNα 1 million IU/week for 6 months, and subsequently became negative for viral marker (HCV-RNA). At age 60, she was diagnosed as having type 2 diabetes; fasting plasma glucose (FPG) was 199 mg/dL and HbA1c 6.9%. Her HbA1c improved with glimepiride 1 mg/day. Because HCV-RNA was again increased, PEG-IFNα 180 μg/week was started at age 61. Due to a taste disorder, the dose was decreased to 90 μg/week two months later and continued for 9 months. During PEG-IFN administration, blood glucose control worsened, but adding buformin (150 mg/day) to her treatment regimen decreased HbA1c from...
At age 62, because HCV-RNA levels had not decreased, PEG-IFN (80 μg/week) plus RBV (600 mg/day) combination therapy was started. Glycemic control rapidly deteriorated; FPG and HbA1c increased to 280 mg/dL and 8.8%, respectively, two months after the initiation of RBV therapy (Fig. 1). One month later, the patient was admitted to our hospital for blood glucose control. On admission, her body mass index was 20.8 kg/m², with no remarkable physical findings. Laboratory data included high blood glucose (FPG 303 mg/dL, HbA1c 9.5%) with slightly elevated hepatic transaminases (AST/ALT 53/60 IU/L). It was noteworthy that she was positive for both anti-GAD and anti-IA2 antibodies. Thyroid hormone levels were normal with slightly elevated TSH. Anti-thyroglobulin antibody (TbAb) and anti-thyroid peroxidase antibody (TPOAb) were positive (Table 1), suggesting autoimmune thyroiditis with subclinical hypothyroidism. Her HLA types included A24, DRB1*0405/0901, DQA1*0302 and DQB1*0401/0303, which confer high susceptibility to T1D. Based on positive autoantibodies against pancreatic islets, T1D was diagnosed.

The PEG-IFN and RBV combination therapy was stopped and intensive insulin therapy was started, resulting in gradual improvement of blood glucose control with 35 units/day of insulin. Five months later, anti-GAD antibody remained positive (31.7 U/mL) with fair blood glucose control (HbA1c 5.5%) using 27 units/day of insulin.

### Discussion

Since IFN was first reported to be effective for HCV infection in 1986 (8), IFN has been widely used for patients with chronic hepatitis C. However, autoimmune diseases, such as autoimmune thyroiditis (9), rheumatoid arthritis (10), autoimmune hepatitis (11), systemic lupus erythematosus (12) and T1D (13), reportedly develop with IFN therapy. In particular, several reports have documented the development of thyroid autoimmune disorders in cases receiving IFN plus RBV combination therapy (14, 15) and the present patient is likely such a case.

T1D is at least in part an autoimmune disease character-
ized by loss of pancreatic β cells with T lymphocyte infiltration of islets (16). IFNα stimulates T-helper (Th)1 lymphocytes which are CD4+ and secrete interleukin-2, IFNγ and tumor necrosis factor β. These cytokines facilitate the generation of CD8+ cytotoxic T cells which injure pancreatic β cells (17). In fact, IFNα is significantly up-regulated in patients with T1D (18). These findings suggest that IFNα is involved in β cell destruction and thereby in T1D development.

In 1992, it was documented for the first time that IFN therapy for chronic hepatitis C can induce T1D (13), and this was followed by similar case reports (reviewed in (19)). Subsequently, PEG-IFN therapy was also reported to induce T1D (5). Therefore, IFN administration is likely to affect Th1 immune reactions, leading to the development of T1D, as discussed above.

The present case was first diagnosed as having type 2 diabetes 7 years after IFN therapy. IFN therapy reportedly worsens insulin resistance, resulting in deterioration of glucose tolerance (20). In our case as well, blood glucose control deteriorated slightly during PEG-IFN therapy, though fair control of blood glucose was achieved with biguanide therapy for chronic hepatitis C (22, 23). RBV administration should be avoided in patients with T1D-susceptible HLA.

References

