CASE REPORT

Hearing Loss as a Complication of Peginterferon Alfa 2a Combination Therapy in a Patient with Hepatitis C Virus Infection

Mohssen Nassiri Toosi MD[1], Mohammad Sadeghi Hassanabadi MD[2]

Department of Internal Medicine[1]and Otolyrngology[2]
Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran.

Coresponder:
Mohssen Nassiri Toosi MD, Associated professor of Gastroenterology, Imam Khomeini Hospital, Tehran University of Medical Sciences

E mail:
mohssen_nasiri@yahoo.com

Tel:
0098 21 801 2992

Fax:
0098 21 225 3635

Abstract

Hearing loss has been reported on interferons therapy. Combination therapy of pegylated (PEG)-IFN alfa2a plus ribavirin is the current optimal therapy for hepatitis C infection. PEG-INF side effect profile is reported similar in different studies, but with the increasing long-term use of PEG-INF several new adverse effects have been recognized. However, hearing loss has only been recorded once. We report a case of sensorineural hearing loss occurring in a patient with chronic hepatitis C treated with PEG-IFN plus ribavirin and recovered partially one month after the discontinuation of PEG-INF. The ototoxicity would be more serious with the use of PEG-INF. Patients on therapy with this drug should be monitored for auditory disability. The ototoxicity is reversible with discontinuation of drug if the diagnosis is made early in the course.

Introduction

Interferon (IFN) therapy has been widely used for the treatment of many systemic disorders including acute and chronic viral illnesses[1], autoimmune diseases[2, 3] and neoplasms.[4, 8] Pegylated-INF an enhanced IFN molecule produced by the covalent attachment of a branched 40-kd polyethylene glycol moiety to IFN alfa-2a (PEG [40kd] IFN alfa-2a) exhibits sustained absorption, a restricted volume of distribution, and reduced clearance compared with unmodified IFN. PEG-INF acts as a direct antiviral agent by regulating the functions of many cells of the immune response system. It plays a role both in the initial response to acute viral infection, and in maintaining and regulating the immune response. The antiviral immune response may also lead to autoimmune pathologic consequences, mediated by antibodies formed in response to viral infection, or by immune complexes produced during an infection. Autoimmune manifestations of hepatitis C infection also occur through other mechanisms, which are still unclear.[9, 10] The common side effects associated with PEG-IFN use are similar to conventional INF therapy and include a flu-like

syndrome, as well as hematologic, infectious, autoimmune, and psychiatric problems[11,12] but auditory complications of IFN administration are rarely reported.[13, 14] We report a case of sensorineural hearing loss induced by PEG-IFN in whom tinnitus was recovered partially 10 days after its discontinuation.

Case report

A 55 year-old woman with fatigue and elevated liver enzymes was diagnosed to have chronic hepatitis C. Her laboratory tests showed: AST 69 IU/L, ALT 105 IU/L, Alk.phos 116 IU/L, Hb 15 g/dl, WBC 6700/ml, PLT 225,000/ml, ESR 11 mm/hr, cholesterol 187 mg/dl, triglyceride 74 mg/dl, Alb 4.5 g/dl, PT 100%, TSH 0.2 IU/L, HBsAg -ve, HBsAb -ve, HbcAb -ve, HCV genotype 1a, HCV-RNA level 380,000 IU/ml, and liver biopsy grade 4/18, stage 2/6 based on modified histologic activity index.

The patient has been treated with PEG-IFN 180 micg weekly through intramuscular injection and ribavirin 1000 mg daily. She took acetaminophen tablets just for the first three injections. She did not get any other medicine. Two months after treatment, she had AST 22 IU/L, ALT 15 IU/L, PT 100%, Alb 4.5 g/dl, Hb 12.8 g/dl, WBC 3,600/mm^3, reticulocyte count 2%, PLT 258,000/mm^3, and TSH 1.5 IU/L. At this time, she realized a right side tinnitus with progressive hearing loss. Her past history was negative for any other systemic or infectious disease. There was not familial history for otologic disease. Her tympanic membrane and otolaryngologic examinations were normal. Conventional audiologic assessment, including pure-tone audiometry, showed bilateral sensorineural hearing loss in 2000 Hz and more frequencies with mean hearing threshold of 45 db Other audiologic assessments were normal. No vestibular dysfunction was found. Auditory disability consisted of tinnitus and moderate high-tone sensorineural hearing loss. The patient did not have sensorineural hearing loss due to other known causes. The average cumulative dose until development of the auditory disability was 2,160 micg. Auditory disability was not associated with leucopenia, thrombocytopenia, hypoproteinemia, proteinuria, and derangement of liver function. Immunological examination (cryoglobulins, anti-nuclear antibody, and anti-smooth muscle antibody) was normal. Because of HCV infection, no steroids were prescribed. PEG -IFN therapy was discontinued because no other potential causes of sensorineural hearing loss were found. After 10 days tinnitus spontaneously recovered and disappeared. Audiometry 2 weeks after drug discontinuation showed 10 db recovery in hearing threshold and serial audiometry during next month revealed progressive recovery in hearing threshold to normal limit.

Discussion

We believe the auditory disability in this case was attributable to interferon because: 1) The high frequency of auditory disability and bilateral involvement are compatible with drug ototoxicity; 2) There was relatively rapid improvement after discontinuation of drug; 3) Appearance of ototoxicity two months after PEG-INF therapy is in support of this idea which ototoxicity to be dose-related, although the critical dose was not reported; 4) The patient had no other potential cause of sensorineural hearing loss. Rare ototoxicity of interferon has been recorded. The auditory disability during IFN therapy was previously observed only by Kanda et al[14], who conducted a prospective study to assess the auditory function in patients receiving IFN. They observed auditory disability in 17/35 patients treated with beta-IFN (including hearing loss in 13 patients), and in 15/38 patients treated with alfa-IFN. Hearing loss and tinnitus disappeared in all patients within 7 to 14 days after discontinuation of IFN. The auditory disability, however, could have been overlooked with interferon therapy because it was often mild and subclinical. beta -IFN seems more ototoxic than alfa -IFN, but this may reflect a difference in administration rather than in the type, because both share a receptor on the cell surface.[15]

A direct ototoxicity is unlikely, while it may be hypothesized that autoimmunity precipitated or probably exacerbated by IFN therapy in an HCV-positive patient is a possible mechanism. In fact with the increasing long-term use of interferon (IFN) in chronic hepatitis C, numerous autoimmune problems have been recognized, such as thyroid diseases [18], type 1 diabetes mellitus[19]. Interferon can induce or enhance autoimmune diseases,[25, 26] and autoimmunity is believed to be one of the major causes of “idiopathic” hearing loss.[27] Hepatitis C virus (HCV) infection has been associated with a plethora of immune and autoimmune disturbances sometimes first triggered by HCV infection and then aggravated by the immunomodulatory action of interferon therapy.[17] The auditory disability often occurred in the late stage of therapy, as does thyroid autoimmune disease during interferon therapy.[28] It is supposed that autoimmunity is a possible mechanism in the pathogenesis of microvascular damage, which was also reported in retinal vascular lesions by alfa-IFN therapy.[16] Moreover, IFN is reported to inhibit the motility of capillary endothelial cells[20] , and to induce the expression of HLA antigens[21] , and affect autoimmune T cells through the induction of intracellular adhesion molecule-1.[22] Moreover, as in ocular autoimmune disease, the microvascular damage may be monolateral[23, 24, 28] with the presence of autoantibodies against the endothelial cells. Rapid improvement of auditory function after discontinuation of interferon suggests microvascular pathogenesis, which was reported in retinal vascular complications after alfa-IFN treatment.

There are other possible mechanisms for hearing loss during interferon therapy. Interaction with antipyretic drugs (salicylate) might be partly responsible for the auditory disability. Thrombocytopenia induced by interferon might have caused a microvascular accident in the inner ear. Direct toxicity to the auditory nerve or hair cells might have occurred because interferon can enhance the excitability of cultured neurons.[29] The interferon has also been shown to have significant effects on central neurons, on the regions of the brain that are important for learning and memory.[30]

Conclusion

We conclude that in HCV-positive patients being treated with PEG-IFN, who complain of hearing loss and tinnitus

during the therapy, IFN treatment should be withdrawn and an audiologic, autoimmune, drugs, and Hematologic assessment should be done. The ototoxicity will be more serious with the use of PEG-INF. Patients on long-term therapy with this drug should be monitored for auditory disability. The ototoxicity is reversible if the diagnosis is made early in the course.

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