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Ocular Findings Before and After Pegylated Interferon Treatment in Chronic Hepatitis B and C Patients

Kronik Hepatit B ve Hepatit C Hastalarında Pegile-İnterferon-Alfa Tedavisi Öncesi ve Sonrası Göz Bulguları

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ABSTRACT

Objective: Interferons are used in the treatments of chronic hepatitis B and C since they inhibit viral replication and have immunomodulatory effects. Common side effects include: flu-like syndrome, hematologic abnormalities, cardiovascular system and gastrointestinal system symptoms, diabetes, autoimmune disorders, pulmonary dysfunction, and suffering from depression. In this study, the development of retinopathy, a rare side effect of interferon, was aimed to be investigated.

Materials and Methods: Forty-three patients with hepatitis B and C followed-up in İzmir Tepecik Training and Research Hospital, Infectious Diseases outpatient clinic were included in the study. Pegylated-interferon-alpha therapy was initiated in all patients. Fundus examination results of patients who completed 48 weeks of treatment were evaluated before and after the treatment.

Results: Diabetic retinopathy (DRP) was determined in a patient before treatment (proliferative DRP on left and right). Arteriosclerotic fundus vessels in another patient were determined. After the treatment, the findings in these patients were still the same. However, retinopathy was detected in fundus examination in one (2.32%) patient, although it was found to be normal before the treatment.

Conclusion: The patients who developed retinopathy due to interferon should be closely monitored, risk factors should be investigated, and if necessary, the treatment should be performed. Discontinuation of interferon therapy is usually required in case of development of retinopathy. *(Viral Hepatitis Journal 2014; 20(1): 1-3)*

Key words: Hepatit B, hepatit C, pegile-interferon-alfa, retinopati

ÖZET

Amaç: İnterferonlar, viral replikasyonun inhibisyonu ve bunun yanı sıra immünomodülatör etkisi ile kronik hepatit B ve C tedavisinde kullanılırlar. Sık görülen yan etkileri arasında grip benzeri sendrom, hematolojik anormallikler, kardiyovasküler ve gastrointestinal sistem semptomları, diyabet, otoimmün hastalıklar, akciğer fonksiyon bozukluğu ve depresyon vardır. Bu çalışmada, interferonların daha nadir görülen bir yan etkisi olan retinopati gelişiminin araştırılması amaçlanmıştır.

Gereç ve Yöntemler: İzmir Tepecik Eğitim ve Araştırma Hastanesi Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Polikliniğinden takipli 43 hepatit B ve C hastası çalışma kapsamına alındı. Hastaların tümüne pegile-interferon-alfa tedavisi başlandı. Tedavileri 48 haftaya tamamlanan hastalar, tedavi öncesi ve tedavi bitiminde göz dibi muayeneleri ile değerlendirildi.

Bulgular: Tedavi öncesi göz dibi bakısında, bir hastada diyabetik retinopati (DRP) -sağda ve solda proliferatif DRP- saptandı, bir diğer hastada ise fundus damarları arteriyosklerotik olarak belirlendi. Tedavi sonrasında ise bu hastalarda aynı bulguların devam ettiği, 1 (%2,32) hastada ise tedavi öncesi olağan bulunmasına karşın, tedavi bitiminde göz dibi muayenesinde retinopati saptandı.

Sonuç: İnterferona bağlı retinopati gelişen hastalar yakından takip edilmeli, risk faktörleri sorgulanmalı ve gerekirse tedavisi yapılmalıdır. Retinopati gelişmesi hâlinde interferon tedavisinin kesilmesi nadiren gerekmektedir. *(Viral Hepatit Dergisi 2014; 20(1): 1-3)*

Anahtar Kelimeler: Hepatit B, hepatit C, pegile-interferon-alfa, retinopati

Introduction

The aim in the treatment of chronic viral hepatitis is to eliminate the virus by stopping viral replication, to achieve improvement of liver histology, and hence, to prevent cirrhosis and hepatoma (1). It was first reported in the 1970s that interferons (IFNs) could be effective in the treatment of chronic viral hepatitis (1). IFNs are natural proteins with a broad biological activity. There are three types of IFNs: alpha, beta and gamma. The production and use of IFNs have increased with recombinant DNA technology. The most widely applied type is IFN-alpha (IFN-α). There are preparations in Turkey as alpha 2a and 2b (1). IFN-α binds specifically to the receptors with high affinity on the surface of target cells. In infected cells, the

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2'-5'-oligoadenylate synthetase system inhibits viral replication via the Mx proteins and double helical RNA-dependent protein kinase, and also provides an immunomodulator effect. It stimulates expression of MHC I antigens, and activates macrophages, natural killer cells and effector cells such as cytotoxic T lymphocytes. Pegylated-IFN-α (PEG-IFN-α) is made by the protein pegylation of IFN-α. It is a long-acting form administered once a week with pharmacokinetics and pharmacodynamics and is superior to the standard interferon. PEG-IFN-α-2a and -2b, which are PEG formulations of IFN-α-2a and 2b, have been developed to reduce the fast clearance of IFN-α-2a and 2b (2). Its most common side effects include flu-like syndrome, hematological anomalies, symptoms of the cardiovascular system and gastrointestinal system, diabetes, autoimmune diseases, pulmonary dysfunction, depression and retinopathy. IFN-α is known to cause autoimmune diseases by activating antibodies. Occurrence of type 1 DM, autoimmune thyroid diseases, psoriasis, hemolytic anemia, rheumatoid arthritis, thrombocytopenia, syndromes such as systemic lupus and autoimmune diseases such as sarcoidosis have been reported to be associated with the use of IFN (3). More rarely, retinopathy side effect has also been reported. This study aims to evaluate the pre-treatment and post-treatment ophthalmic findings in chronic hepatitis patients who were given PEG-IFN-α treatment and followed up at the Tepecik Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology, Hepatitis outpatients clinic.

Material and Methods

Forty-three hepatitis patients followed up in the İzmir Tepecik Training and Research Hospital, Department of İnfectious Diseases and Clinical Microbiology were enrolled in the study. Thirty-three (76.7%) patients were followed up for hepatitis B, and 10 (23.3%) were followed-up for hepatitis C.

It was planned that 20 (60.6%) out of the 33 hepatitis B patients would receive PEG-IFN-α-2a treatment, and 13 (39.4%) of them would receive PEG-IFN-α-2b treatment. It was planned that 6 (60%) out of 10 hepatitis C patients would receive PEG-IFN-α-2a treatment, and 4 (40%) of them would receive PEG-IFN-α-2b treatment. PEG-IFN-α treatment was administered subcutaneously once a week to all patients. Those patients whose treatment had to be stopped due to various side effects, particularly hematological, were excluded from the study. Treatment of the patients included in the study was completed in a total duration of 48 weeks. The patients were evaluated with fundus examination before and after the treatment.

Results

Forty-three cases consisting of 17 female subjects and 26 male subjects with an average age of 42.1 years were evaluated. Of these cases, 33 (76.7%) patients were initiated PEG-IFN-α treatment for hepatitis B, and 10 (23.3%) patients were initiated PEG-IFN-α treatment for hepatitis C. During the pre-treatment fundus examination, diabetic retinopathy (DRP) -proliferative DRP in the right and left eye- was detected in a patient diagnosed with chronic hepatitis C with previously known diabetes, and in another patient diagnosed with chronic hepatitis B, and fundus vessels were found to be arteriosclerotic.

It was observed that the same findings continued in these patients after the treatment, however in 1 (2.32%) hepatitis C patient without a history of chronic disease (DM, HT, etc.) who received PEG-IFN-α-2a (180 µg/once a week) treatment, the pre-treatment eye examination was found normal, and retinopathy was detected in the post-treatment eye examination. In this patient, diabetes and hypertension were not detected in the follow-ups during his/her PEG-IFN-α treatment. Fundus examinations in the 4th and 8th weeks after the patient stopped taking the drug provided normal results.

Discussion

Retinopathy associated with IFN was first identified in 1990 in a 39-years-old patient by Ikebe et al. In this patient, retinal hemorrhage and cotton-wool spots occurred following intravenous administration of IFN (4).

The mechanism of retinopathy is associated with IFN, but the possibility of impairment of retinal microcirculation is considered (5). It has been shown that existing arteriosclerosis can affect microcirculation, and can play a triggering role on the retinopathy induced by IFN. The most common risk factor in patients who develop retinopathy is hypertension (6,7).

The incidence of retinopathy associated with IFN varies between 18% and 86%. This situation can be explained by causes such as IFN dose, systemic diseases, frequency of eye examinations, and underlying retinal vascular diseases (8). In this study, retinopathy was detected in only 1 (2.32%) patient at the end of the treatment. The fact that this was below the percentage shown in the literature could be due to the fact that the average age of the study subjects was 42.1, and systemic diseases such as hypertension or diabetes mellitus are less common in this age group, and hence, the conditions that pose a risk for retinopathy are decreased.

Cotton-wool spots and surface retinal hemorrhages were seen in the posterior pole and around the optical nerve in retinopathy were associated with IFN. In a study by Jain et al., retinal lesions in all patients were found to be asymptomatic and reversible (9). In this study, although none of the patients had any complaints, eye examinations were performed for control at the end of their treatments.

Retinopathy was found in one patient with chronic hepatitis C infection. Fundus examinations in the 4th and 8th weeks after the patient stopped taking the drug revealed normal results. In a study by Okuse et al., it was reported that 14 out of 73 patients who were given IFN-α-2b and ribavirin combination treatment for chronic HCV developed retinopathy. In 13 of these 14 (93%) patients, retinopathy developed within 12 weeks after the beginning of treatment. In 10 (71%) patients, retinopathy regressed within 4-8 weeks during treatment. This situation shows that the treatment can be continued in many patients despite retinopathy (6).

In the latest studies, the eye findings due to HCV infection are explained by dry eye syndrome in Sjögren syndrome, vasculitis induced by HCV, or ischemic retinopathy due to

IFN (10). Furthermore, in patients with risk factors such as diabetes mellitus and hypertension, the importance of regular ophthalmologic examinations during PEG-IFN and ribavirin treatment is emphasized (10,11,12). Although the frequency of reversible retinopathy is higher, very rarely, cases result in serious and irreversible loss of vision. It is also very important to determine when the treatment will be ended with regular examinations (12).

In hepatitis B infection, there were not any very serious eye findings other than dry eye syndrome (10).

The hepatitis B patients in our study did not develop retinopathy after PEG-IFN-α treatment.

As a result, patients who develop retinopathy due to IFN should be followed up, and their risk factors should be questioned, and they should be treated if necessary. If retinopathy develops, it may rarely be required to stop IFN treatment.

Conflict of interest: None declared.

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