Cardiotoxic properties of interferon

Exacerbation of atrio-ventricular block during treatment of hepatitis C with peginterferon – a case report

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Abstract: The authors reviewed cardiac adverse events during interferon therapy. The significance of pre-existing cardiac disease (coronary artery disease, chronic heart failure or cardiac arrhythmias) must be considered in patient qualification for this treatment. A case of a 55-year–old woman with chronic hepatitis C, qualified to peginterferon therapy in our hospital, is presented. This patient did not have cardiac diseases diagnosed previously. Atrio-ventricular (AV) conduction disturbances in the form of second degree AV block were diagnosed during peginterferon therapy; the intensity of these disturbances diminished when treatment was paused. A pacemaker had to be implanted to enable the patient to continue the treatment without these side effects.

Key words: conduction disturbances, hepatitis C, peginterferon

INTRODUCTION

Interferons are 143-146 amino-acid cytokines produced by leucocytes (IFN-α), fibroblasts (IFN-β) or lymphocytes T (IFN-γ) following stimulation by viruses, some bacterial or protozoan antigens, as well as mitogens or synthetic polymers. These inflammatory mediators were applied in treatment of chronic viral diseases (hepatitis B, hepatitis C, hepatitis D, infection with genital papilloma virus), as well as some neoplasms such as malignant melanoma, multiple myeloma and chronic myeloid leukaemia. Thanks to genetic engineering achievements the synthesis of interferon for medicinal purposes became far cheaper, than at the time when they were being separated from leukocytes, fibroblasts or transformed lymphoid cells – this technology enabled their considerably wider application.

Interferons do not have any direct antiviral properties, they activate some enzymes enabling the decline of genetic material of viruses in the cell, leading to the so-called "antiviral state". However, their anti-neoplastic action results in strong stimulation of the synthesis of cancer surface antigens on neoplastic cells what makes them more recognizable and sensitive for attack by immunologic mechanisms. Augmented phagocytosis, activation of macrophages, increased cytotoxicity of lymphocytes T, K cells and NK cells or the induction of cytokine expression, such as IL-1, IL-6, TNF-α are the examples of interferon influence on the immunological system. Hence flu–like syndrome is frequent at the beginning of therapy with interferon and is one of the troublesome adverse effects of this treatment.

"Conventional" interferon α used in last decades is characterized with suboptimal pharmacokinetic properties: inconvenient administratio pattern (3 times a week) and with considerable fluctuations of activity during therapy. By attaching to the particle of interferon α a 40kDa molecule of polythene glycol improves the pharmacokinetic parameters and dosing once a week – the effective concentration of peginterferon (pegIFN) is stable through 7 days.

The patient with cardiovascular disease must be consulted by a cardiologist before commencing therapy with interferon, because this treatment can lead to exacerbation of such entities like heart failure, coronary artery disease or arrhythmias. Balancing the benefits and risks leads to a decision whether to commence or resign from therapy with interferon. The prevalence of life threatening complications during the treatment with „conventional" interferon is estimated on 0.1–1.0%, but cardiac serious adverse effects are only a certain fraction of this number, besides endocrinological, pulmonological or renal problems [1]. According to statistics published by Sonnenblick et al. who had focused on cardiotoxicity of this group of compounds, the most frequent disorders are ventricular arrhythmias (58%), acute coronary syndromes (21%), cardiomyopaties (12%), while less frequent are conducting atrio-ventricular conducting abnormalities, congestive heart failure or a sudden

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Received: December 18, 2006. **Accepted in final form:** March 25, 2007.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2007; 117 (1-2): 49–52

cardiac death [2]. The less dangerous adverse events during therapy with interferon are: tachycardia, arterial hypertension, hypotonia and benign arrhythmias. It should be emphasized, that the toxicity of interferon is age, dose and type dependent but above all is dependent on previous cardiological burden. Fukuhara's et al. studies on values of the arterial pressure, its twenty-four hour profile before and during treatment with INF in patients with chronic viral hepatitis, but without cardiovascular diseases, did not demonstrate the adverse effect of this treatment in the aforementioned parameters [3]. Satori et al. in the similar group of patients estimated the impact of therapy with IFN on the decrease of the left ventricle ejection faction. These authors, stated on the basis of radionuclide examinations made three times (before, in the route and 3 months after finishing treatment with interferon), that a maximum drop of the ejection faction appears during treatment, drops by 10% and following completion of interferon therapy this parameter returns to its initial value [4]. Therefore, basing on previous studies, it is recommended to perform cardiological consultation mainly in patients with cardio-vascular illness diagnosed earlier or in case when interview or physical examination implies presence of such illness. In the situation, when atrio-ventricular block I* (PQ interval >0,2 s), intervenricular conduction abnormalities , or numerous extrasystoles are present in resting ECG, and the patient reports collapsing, loss of consciousness or vertigo in his history – before the decision on commencing interferon therapy one should perform a Holter 24-hour ECG monitoring. In patients with myocardial infarction in their history, with electrocardiographical signs of past myocardial infarction (pathological Q waves, negative T waves, lack of the progression of R waves amplitude in precordial leads), but primarily in patients reporting retrosternal pains, percutaneous or surgical interventions on coronary vessels or being under current treatment due to angina pectoris must be assessed using an electrocardiographic exercise test. Changes in the ST segment during exercise on the treadmill, the load of tolerated effort, the changes in arterial pressure and pulse are the parameter which help the consulting cardiologist in making decision whether to verify the result of a stress testing by coronary angiography. For assessment of the function of the left ventricle myocardium at patients with symptoms of heart failure (short breath, lowered tolerance of effort, oedema of lower limbs) one should make an echocardiographic examination. The value of the left ventricle ejection faction <40% shows impaired function of the cardiac muscle. Therapy with interferon can potentially cause a decrease of cardiac function and at the same time diminish the value of the ejection faction by about 10%.

In the case of exacerbation of cardiovascular signs one should stop therapy with interferon and consider the possibility of its continuation after intensifying pharmacotherapy or applying invasive treatment.

A patient showing cardiotoxic action of peginterferon, whose test results recovered thanks to cardiac intervention, is described in the next part of the article.

CASE REPORT

A 55-year-old woman with chronic C hepatitis after 4 months treatment with peginterferon in a dose of 80 μg once a week and ribavirin with a dose at start of 1000 mg/day, and then – due to anaemia – reduced to 600 mg/day, was admitted to the Infectious Diseases Department in our hospital because of self–reported palpitations of the heart and reporting of irregular heartbeat.

Hepatitis C was diagnosed in 1994; in 1996 a biopsy of the liver was made. The degree of the inflammatory process, so-called grading (G), was microscopically assessed as small – 2 on the scale from 0 to 4, and the degree of fibrosis advancement , so-called staging (S), at 3 on the scale from 0 to 4 which means advanced fibrosis (grade 4 is cirrhosis) was present. Alanine transaminase activity (ALAT) was – 300 u/ml. First therapy with interferon lasted for 6 months, this therapy was being administered in a dose of 3.000.000 units (u) 3 times a week. This therapy was ineffective. After a half-year intermission she was treated again with interferon 3 times a week in a dose of 5.000.000 u. The following attempt at therapy with interferon of 3 times a week at a dose of 3.000.000 u. and ribavirin 1000 mg/day was taken in 1999. After completed the aforementioned therapies an increase in the ALAT activity was observed. In 2000 a biopsy of the liver was made again (G-2 S-3), ALAT activity was 100 u/ml. In 2003, after viremia assessment (HCV RNA -1.980.000 copies/ml) was done, the following therapy with peginterferon 80 μg once a week and ribavirin at first dose 1000 mg/day, and then due to anaemia – 600 mg/day – was administered. After 12 weeks a decrease of viremia to 600 copies/ml was observed. In the fourth month of combined therapy the patient was admitted to the hospital in order to assess the effects of therapy.

In the physical examination apart from an enlarged liver no abnormalities were found.

In the laboratory test results: leucocyte count – 2.5 x 10^3/μL, neutrofiles – 1.01 x 10^3/μL, lymphocytes – 1.00 x 10^3/μL, platelets – 143 x 10^3/μL, erythrocytes – 4.11 x 10^3/μL, hematocrit – 36%, haemoglobin – 11.7 g/dl, CRP – 2.84 mg/l, ALAT – 25 u/l, TSH – 3 uIU/ml, K – 4.14 mmol/ml, Na – 138 mmol/ml, Cl – 101 mmol/ml, Mg – 2.24 mg/dl, glucose – 77 mg/dl. In the ultrasound examination of the abdomen there were no abnormalities, in the echocardiographic examination – normal dimensions of the heart chambers and the thickness the left ventricular wall, symmetrical contractility with ejection fraction of the left ventricle of 60%, valves without organic changes and with normal flows were found. In a 24-hour ECG Holter monitoring made on the first day of hospitalization – 59 missed beats and 4 episodes of bradycardia in the mechanism of the AV block II° – Wenckebach's period were found. Interferon therapy was stopped for 2 weeks and again a Holter record of ECG for 24 hours was registered: in the night-time AV block I° with the PQ interval equal to 440 ms, 5 short (for 6 beats) of episodes of bradycardia and 113 missed beats in the mechanism of Wenckebach's period. Af-

ter resuming therapy, a subsequent 24-hour ECG monitoring was done, which revealed AV block I° (PQ interval = 440ms), one episode of AV block II° 2:1 and 38 missed beats in the mechanism of the AV block II° – Wenckebach's period (the longest RR interval = 2159 ms), as well as one short episode of bradycardia – 5 beats with a frequency of 34/min in the mechanism of AV block II° – Wenckebach's period. Rhythm and conducting abnormalities were asymptomatic. There were no depressions of the ST segment in ECG. Exercise stress test was negative, stopped after reaching the pulse limit at a load of 5 METs – in the ECG without effort-induced changes in the ST segment. In the "recovery" period a drop of blood pressure to 85/45 mmHg was registered.

After the cardiological consultation the patient was qualified for pace-maker implantation – a cardiostimulator was implanted 5 months before the planned end of therapy with interferon. An artificial pacemaker working at the VDD mode was implanted the patient (Axios SLR, Biotronik) with the passive fixation of chamber electrode (Selox ST 60/15-BP, Biotronik). The operation and post-operation period were without complications. The atrio-ventricular delay was fixed on 140 ms. Subsequent ECG Holter monitoring made 3 months after completion oftherapy with interferon demonstrated, that 16.5% of heart beats was stimulated out by the artificial pacemaker. The so-called "classical" risk factors of ischemic heart disease were absent in this patient.

DISCUSSION

Case reports of total atrio-ventricular blocks are available in medical literature – previously described conduction disturbances occurred both in the first days of therapy, as well as after passing over one month from commencement of therapy. An interesting problem is that dangerous conduction abnormalities were observed both at taking low as well as high doses of interferon [5, 6, 7]. In the former case, halting therapy was enough to restore correct AV conduction, and in the latter case additional application of prednisolone was needed. The authors of these case reports emphasize that interferon therapy must be particularly accurate monitored in persons with data showing previous damage to the stimulogenic system [8]. Recently, data comparing the effectiveness and the safety of therapy with peginterferon and ribavirin in 283 patients with hepatitis C and 814 patients with hepatitis B treated with peginterferon and lamivudine was published [9, 10]. In none of cited studies any cardiac complications in the course of described therapy were observed.

Infectious background of impaired AV conducting should be also taken into consideration in patients infected with hepatitis C virus (HCV). The analysis made concurrently by 10 hospitals in Japan demonstrated, that among 697 patients infected with HCV – the 28.4% of them had in the ECG AV block I° and 41.2% – intraventricular conducting abnormalities under the form of right branch bunch block [10]. Mechanism of disadvantageous action of the interferon on stimulogenic system are not explained in a reliable way. Quoted data can suggest, that therapy with interferon can reveal preceding asymptomatic disturbances of the stimulogenic system, which might have had infectious origin, which probably took place in our patient.

REFERENCES

1. Dusheiko G. Side effects of alfa interferon in chronic hepatitis C. Hepatology 1997; 26 (Suppl 1):112S-121S.
2. Sonnenblick M, Rosin A. Cardiotoxity of interferon. A review of 44 cases. Chest 1991; 99: 557-561.
3. Fukuhara M, Matsumura K, Ohmori S, et al. Effects of interferon on circadian changes in blood pressure and heart rate variability in patients with chronic hepatitis. Am J Hypertens. 1999; 12: 519-523.
4. Satori M, Andorno S, La Terra G, et al. Assessment of interferon cardiotoxity with quantitative radionuclide angiocardiography. Eur J Clin Invest, 1995, 25: 68-70.
5. Teragawa H, Hondo T, Amano H, et al. Cardiogenic shock following recombinanat alfa-2b interferon therapy for chronic hepatitis C. A case report. Jpn Heart J. 1996; 37: 137-142.
6. Parrens E, Chevalier JM, Rougier M, et al. [Third degree atrio-ventricular block induced by interferon alpha. Report of a case]. Arch Mal Coeur Vaiss. 1999; 92: 53-56.
7. Tsushima K, Yamaguchi S, Furihata K, et al. [A case of renal cell carcinoma complicated with intestinal pneumonitis, complete A-V block and pleural effusion during interferon-alpha therapy]. Nihon Kokyuki Gakkai Zasshi. 2001; 39: 893-898.
8. Masutani M, Suzui J, Matsuda T, et al. [Changes of 24-h Holter monitoring recordings in association with interferon alpha therapy for chronic hepatitis]. Nihon Kokyuki Gakkai Zasshi. 1998; 95: 1222-1228.
9. Mangia A, Santoro R, Minerva N, et al. Peginterferon Alfa-2b and ribavirin for 12 vs. 24 weeks in HCV genotype 2 or 3. N Eng J Med. 2005: 352: 2609-2617.
10. Lau G, Piratvisuth T, Xian Luo K, et al. Peginterferon alfa-2a, lamivudine, and the combination for HbEAg-positive chronic hepatitis B. N Eng J Med. 2005; 352: 2682-2695.
11. Matsumori A, Ohashi N, Hasegawa K, et al. Hepatitis C virus infection and heart diseases – a multicenter study in Japan. Jpn Circ J. 1998; 62: 389-391.