TREATMENT OF CHRONIC HEPATITIS C IN HEMOPHILIC PATIENTS

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Summary. – Chronic hepatitis C infection is common among hemophiliacs in all the developed countries. Since 1996, only alpha-interferon (alpha-IFN) in monotherapy has been used for the treatment of chronic hepatitis C in hemophiliacs (6 patients). In Czech Republic a combination therapy with alpha-IFN and ribavirin has been used since 1999 (13 patients). Finally, a combination therapy with pegylated alpha-IFN (PEG-alpha-IFN) and ribavirin is being used since 2001 (still 3 patients). In all cases, the treatment lasted 48 weeks. A sustained virological response (SVR, defined as an undetectable serum HCV RNA level 24 weeks after the treatment was completed) was not achieved in any of 6 patients treated with alpha-IFN alone. A combination therapy with alpha-IFN and ribavirin yielded better results: four of eight patients still untreated with alpha-IFN (naive patients), one of two relapsers, and one of three non-responders to previous alpha-IFN monotherapy achieved SVR. So far the combination therapy with PEG-alpha-IFN and ribavirin has been used only in 3 patients. SVR was achieved in one patient who had relapsed after the combination therapy with IFN-alpha and ribavirin, and in 1 of 2 non-responders to this therapy. We conclude that the efficacy and tolerability of the treatment of chronic hepatitis C in hemophiliacs did not differ from that of chronic hepatitis C in other patients.

Key words: chronic hepatitis C; hemophilia; alpha-interferon; pegylated alpha-interferon; ribavirin

Introduction

Of various types of hemophilia, a lifelong bleeding disorder, the most common are caused by an inherited deficiency of the coagulation factor VIII or IX (F VIII, F IX). Modern treatment of hemophilia has begun in 1970's with the availability of the plasma concentrates of F VIII, and later F IX. However, the concentrates produced from a pooled plasma obtained from thousands of donors were invariably contaminated with Hepatitis B virus (HBV) or Hepatitis C virus (HCV) and they caused post-transfusion hepatitis in practically all patients with hemophilia who had received them. Chronic hepatitis was common but was thought to be relatively mild and non-progressive, so that the benefits of concentrates seemed to outweigh the risk. Such an optimism proved to be dramatically short-lived when, at the beginning of the 1980's, it has been discovered that 60–70% of severe hemophilia patients in Western Europe and in the United States were infected with Human immunodeficiency virus (HIV) contaminating plasma concentrates (Mannucci and Tuddenham, 2001).

The majority of hemophiliacs in the most developed countries are now treated with recombinant coagulation factors VIII or IX, which do not carry the risk of transmission of viral infection. However, with exception of newborn hemophiliacs, the vast majority of Czech adult hemophiliacs have to rely on antiviral treatment with F VIII and F IX concentrates.

Clinical studies conducted in the Netherlands (Triemstra *et al.*, 1995) and the United Kingdom (Darby *et al.*, 1997) in

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Abbreviations: alpha-IFN = alpha-interferon; PEG-alpha-IFN = pegylated alpha-IFN; ALT = alanine transaminase; ETBR = end of treatment biochemical response; ETVR = end of treatment virological response; F VIII, F IX = factor VIII, factor IX; HBV = Hepatitis B virus; HCV = Hepatitis C virus; HIV = Human imunodeficiency virus; MU = megaunit; SBR = sustained biochemical response; SVR = sustained virological response; subcutaneously = s.c.

the 1990's have clearly shown a high mortality rate of hemophiliacs resulting from decompensated liver cirrhosis and hepatocellular carcinoma as a result of chronic HCV infection with or without coincident HIV coinfection. Thus the efforts of hepatologists to treat hepatitis C even among hemophiliacs should be understood as attempts to forestall the terminal stages of HCV infection.

Recently, the therapy of chronic hepatitis C has greatly progressed. The rate of SVR has increased significantly in the late 1990s with the introduction of a combination of alpha-IFN with ribavirin (Poynard *et al.*, 1998; McHutchison *et al.*, 1998) or a combination of PEG-alpha-IFN with ribavirin (Manns *et al.*, 2001; Fried *et al.*, 2002).

The treatment of hemophilic patients with chronic hepatitis C with various combinations of alpha-INF, PEG-alpha INF and ribavirin was based on recommended treatment regimens for general population of patients with chronic hepatitis C (EASL International Consensus Conference on Hepatitis C, 1999; National Institutes of Health Consensus Development Conference Statement, 2002).

The aim of this study was a retrospective evaluation of the efficacy of different treatment regimens applied to chronic hepatitis C patients with hemophilia in 1996–2003.

Materials and Methods

Patients and alpha-IFN treatment. The results of the treatment of hemophilic patients with chronic hepatitis C with different therapeutically regimens were evaluated at the Department of Infectious Diseases and the Department of Clinical Hematology, University Hospital Brno, Brno, Czech Republic, in 1996–2003. Monotherapy with alpha-IFN was applied to 6 patients since 1996. These patients received 3 megaunits (MU) of recombinant alpha 2b-IFN (Intron-A™, Schering-Plough CO., Ireland) subcutaneously (s.c.) 3 times weekly for 48 weeks. Thirteen patients (8 patients without a history of treatment with alpha-IFN (naive patients), 3 non-responders to alpha-IFN monotherapy and 2 relapsers after alpha-IFN monotherapy) were treated in 1999–2002. All of them received 3 MU of a recombinant alpha 2b-IFN (Intron-A™, Schering-Plough Co., Ireland) s.c. 3 times weekly and ribavirin (Rebetol™, Schering-Plough Lab. N.V., Belgium) orally twice a day. The total daily doses of ribavirin were 1000 mg for patients who weighed less than 75 kg and 1200 mg for those who weighed 75 kg or more. Both drugs were started and stopped at the same time and were administered for 48 weeks. Since 2001, we have had an opportunity to treat patients who have not achieved sustained serum negativity of HCV RNA after a course of alpha-IFN and ribavirin (relapsers and non-responders). These patients were treated with a combination of PEG-alpha 2a-IFN (Pegasys™, F. Hoffmann-La Roche Ltd., Switzerland), 180 μg weekly, and ribavirin (Copegus™, F. Hoffmann-La Roche AG, Switzerland), 800 mg daily for 48 weeks. We disposed of complete treatment results for one relapsing patient and for two non-responders.

Response definition. Before assessing the success of the treatment of the patients with chronic hepatitis C, the following parameters should be defined: virological (the presence of HCV RNA in the serum), biochemical (the serum alanine transaminase (ALT) activity), and histological (grades and stages of the liver inflammatory process). Based on the results of these examinations we speak of virological response (negativity of the serum HCV RNA), biochemical response (normalization of ALT), and histological response (significant reduction in the grade of inflammation and fibrosis stage using various scoring systems). In the case of hemophiliacs, liver biopsies are, as a rule, avoided, as the procedure requires a very expensive hematological preparation and a risk of substantial bleeding cannot be completely eliminated. Therefore liver biopsies were not conducted on any of our patients.

Assessing the success of any treatment is highly dependent on the moment at which we register the treatment effect. There is a distinction between "the virological or biochemical response at the end of the treatment" (ETVR, ETBR) and "the sustained virological or biochemical response" (SVR, SBR) which are assessed 24 weeks after completion of the treatment. The response at the end of the treatment is always markedly stronger than the sustained response as a significant portion of the initially successfully treated patients relapse either in virological (a reappearance of HCV RNA in the serum) or biochemical (a renewed increase in ALT) sense. We then group the patients according to treatment results as follows: (i) a group with a lasting response (responders); a group with an initial response and a subsequent relapse (relapsers); (iii) a group with neither an initial nor a lasting response (non-responders) (EASL International Consensus Conference on Hepatitis C, 1999).

Virological testing. Chronic HCV infection was tested in all patients by various commercially available assays of HCV antibodies (third generation ELISA) and was confirmed by the presence of HCV RNA in the serum by PCR (Amplicor™, Roche, Switzerland). Each patient's HCV serotype was determined before the treatment (Murex HCV Serotyping 1–6 Assay™, Murex, England). It is generally accepted that serotyping results are in accord with the genotyping ones. Among our patients, the most common form of the infection, type 1, clearly dominated. Only one patient was recorded as having the type 5 virus infection, which is rare in the Czech Republic. The basic characteristic of the patients is given in Table 1.

Results and Discussion

We demonstrated that the monotherapy of the patients with chronic HCV with alpha-IFN was almost entirely ineffective (Table 2). This was particularly true for the patients infected with the genotype 1 virus, which occurred in almost all the patients (5 of 6, with the virus type in the remaining patient not identified by serotyping). In two of six patients the serum HCV RNA was eradicated during the therapy. However, after cessation of the treatment, there appeared a virological relapse with the accompanying reappearance of the serum HCV RNA. Therefore, none of the patients that had undergone this therapy demonstrated a sustained eradication of viral replication.

Table 1. Characteristics of the group of patients

Treatment-patients	No. of patients	Age of patients	HCV serotypes
IFN-N	6	19, 24, 25, 25, 37, 52	Type 1 (5 patients), unknown (1 patient)
IFN+RBV-N	8	18, 24, 24, 27, 36, 48, 53, 56	Type 1 (7 patients), type 5 (1 patient)
IFN+RBV-R	2	21, 24	Type 1 (2 patients)
IFN+RBV-NR	3	24, 25, 39	Type 1 (2 patients), unknown (1 patient)
PEG-INF+RBV-R	1	29	Type 1
PEG-IFN+RBV-NR	2	26, 55	Type 1

N = naive, previously untreated patients; R = relapsers; NR = non-responders.
For other abbreviations see their list at the front page.

Table 2. Treatment results

Treatment	ETBR	SBR	ETVR	SVR
IFN-N	4/6 (67%)	0	2/6 (33%)	0
IFN+RBV-N	7/8 (88%)	6/8 (75%)	5/8 (63%)	4/8 (50%)
IFN+RBV-R	2/2 (100%)	1/2 (50%)	2/2 (100%)	1/2 (50%)
IFN+RBV-NR	2/3 (67%)	2/3 (67%)	1/3 (33%)	1/3 (33%)
PEG-IFN+RBV-R	1/1 (100%)	1/1 (100%)	1/1 (100%)	1/1 (100%)
PEG-IFN+RBV-NR	2/2 (100%)	1/2 (50%)	2/2 (100%)	1/2 (50%)

For the abbreviations see Table 1 and their list at the front page.

With the addition of ribavirin, which has notable immunomodulatory effects, the efficacy of the antiviral alpha-IFN treatment markedly increased. At end of the treatment, five of eight patients had no detectable HCV RNA. In the following 24 weeks of monitoring, one patient exhibited a virological relapse. Therefore, SVR was registered in four out of eight patients (50%).

So far only three patients were treated with combined PEG-alpha-IFN and ribavirin. SVR was observed in one patient who had relapsed after the combined treatment with alpha-IFN and ribavirin and in one of two non-responders to this combination therapy.

There is not much information in the literature on the effect of the treatment of chronic hepatitis C patients with hemophilia. The results of pilot studies indicate a very little effect of the alpha-IFN monotherapy in such a patients (Peerlinck *et al.*, 1994; Telfer *et al.*, 1995; Hanley *et al.*, 1996; Rumi *et al.*, 1997; Laursen *et al.*, 1998). Such a low efficacy has been explained by the presence of a part of patients in treatment groups with HIV co-infection, and by the fact that treatment lasted only 6 months in a majority of cases.

In a large-scale French multi-centered study, 58 hemophiliacs have been treated with 3 MU of alpha-IFN in a 12-month course (Beurton *et al.*, 2001). This was followed by a 24-month monitoring period. Thirty-nine (67%) of these patients were infected with HCV genotype 1a or 1b. An unusually high number of patients (24, 41.4%) did not complete the treatment due to adverse effects. This particular group under study (58 hemophiliacs) ended up in this way due to unusual caution of the authors and to the fact that the intensity of adverse effects was not, in most cases, so great as to lead to termination of therapy in other patients not suffering from hemophilia. Deserving special attention is the detection of the coagulation factor VIII inhibitor in the seventh month of the treatment with alpha-IFN and its eradication one month after the end of treatment. There was, however, no bleeding associated with this event. Thirty-four patients completed the entire treatment project, of which eight exhibited sustained negativity of serum HCV RNA. Thus 14% of the original 58 patients were successfully treated.

None of the group of 6 patients treated with alpha-IFN monotherapy for 48 weeks achieved sustained elimination of viral replication. As it is a very small group of patients, comparisons with literature data are not possible. Because the study involved mainly patients infected with the unfavorable virus type 1 (5 cases, in 1 case the type was not identified), these poor results are not surprising.

There is very little information in the literature concerning the hemophiliacs infected with hepatitis C treated with a combination of alpha-IFN and ribavirin. The largest group of patients treated in this way originated from the USA (Fried *et al.*, 2002). The study involved total 113 patients treated with 3MU of alpha-IFN (monotherapy) for 48 weeks three times a week or with a combination of alpha-IFN (at the same dosages) and ribavirin (1000 mg daily). If serum HCV RNA was not eliminated by the 12th week of monotherapy, the combination therapy was started up. The after-treatment follow-up period lasted 24 weeks. All patients were HIV-negative. The study group also included children and adolescents of the age of 13. At the end of the treatment 18 of 56 (32%) patients treated with the combination therapy were negative for serum HCV RNA while only 6 of 57 (11%)

of those treated with alpha-IFN in monotherapy were negative for serum HCV RNA. Sixteen (29%) patients exhibited SVR, while only four (7%) patients of those treated with alpha-IFN alone did so. A definite prevalence of combination therapy over monotherapy was statistically significant (P = 0.027). It is interesting to note the markedly higher occurrence of SVR among the youngsters under 18 of age (10/17, 59%) as compared to adults (6/39, 15%, P = 0.001). Thirty-nine patients with hemophilia or von Willebrand disease were treated in Sweden with a combination therapy using alpha-IFN and ribavirin for 6 months (Lethagen *et al.*, 2001). At the end of the therapy 30 of 39 patients (77%) were negative for the serum HCV RNA, and 14 (36%). of the negatives remained so after six months A treatment failure was significantly more common among patients infected with HCV genotype 1 than among those infected with other HCV genotypes (P = 0.0003).

In our study, four of eight previously untreated patients (50%) treated with a combination of alpha-IFN and ribavirin exhibited SVR. As in the group mentioned above, seven of eight patients were infected with an unfavorable type 1 of the virus, the results are promising. However, due to a low number of patients their significance is open.

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