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# EFFICACY OF ALPHA-INTERFERON MONOTHERAPY AND COMBINATION OF ALPHA-INTERFERON AND RIBAVIRIN IN CHRONIC HEPATITIS C PATIENTS

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A b s t r a c t

We compared the efficacy of alpha-interferon monotherapy for 6 or 12 months in still untreated (naive) chronic hepatitis C patients. We compared the results of combination therapy with alpha-interferon and ribavirin in patients who relapsed after the previous alpha-interferon monotherapy (relapsers) or not responded to alpha-interferon monotherapy (non-responders). The effect of antiviral therapy was retrospectively assessed on 131 naive patients with chronic viral hepatitis C who were treated with alpha-interferon in dosages of 3 MU three times a week; 48 of them in the course of 6 months (group A), and 83 for 12 months (group B). Seventeen relapsers (group C) and 16 non-responders (group D) underwent subsequent combination therapy using alpha-interferon (in the same dosages) and ribavirin (1.0 or 1.2 grams daily) for 12 months. Sustained virological response (negativisation of nucleic acid of hepatitis C virus in serum 24 weeks after end of treatment) was achieved at 6 %, 19 %, 29 %, and 6 % of patients from groups A-D. The treatment results of combination therapy in relapsers were significantly better ($p<0.05$) than in non-responders. There were no significant differences between naive patients who received alpha-interferon monotherapy for 6 or 12 months. Sixty-one % of the patients from group B with low pretreatment viremia ($\leq$ 2 MEq/ml) experienced an end-of-treatment virological response, which was significantly more often than among patients with high viremia ($p<0.05$). Sustained virological response was, however, not significantly different (17 % versus 8 %). It was impossible to assess dependence of response on the viral serotype, as type 1 was entirely dominant (88 % in group A; 90 % in group B; 92 % in group C; and 100 % in group D). There were no significant differences in the treatment results between naive patients treated with alpha-interferon for 6 or 12 months. In relapsers, combination therapy with alpha-interferon and ribavirin was more effective than in non-responders.

K e y w o r d s

Chronic hepatitis C, Alpha-interferon monotherapy, Combination of alpha-interferon and ribavirin

A b b r e v i a t i o n s

alpha-INF, alpha interferon; ALT, alanine transaminase; anti-HCV, antibodies to HCV; CAH, chronic active hepatitis; CAH/LC, advanced fibrotic chronic active hepatitis; CHC, chronic

hepatitis C; CPH, chronic persistent hepatitis; ELISA, enzyme-linked immunosorbent assay; ETBR, end-of-treatment biochemical response; ETVR, end-of-treatment virological response; HCV, hepatitis C virus; HCV RNA, ribonucleic acid of HCV; LC, liver cirrhosis; MEq/ml, mega equivalents per millilitre; MU, mega units; PCR, polymerace Chin reaction; SBR, sustained biochemical response; SVR, susteained virological response

## INTRODUCTION

Hepatitis C is a major health problem. The global prevalence of chronic hepatitis C (CHC) is estimated to average 3 %. In industrialized countries, hepatitis C virus (HCV) accounts for approximately 20 % of cases of acute hepatitis, 70 % of cases of chronic hepatitis, 40 % of cases of end-stage cirrhosis, 60 % of cases of hepatocellular carcinoma, and 30 % of liver transplants. All these figures indicate the extraordinary importance of HCV infection (*1*)

The first attempts at treating CHC date from the period when the agent of the disease was unknown and was temporarily designated as post-transfusion non-A, non-B hepatitis. From that time the treatment of choice has been alpha-interferon (alpha-IFN) in monotherapy, and, in recent years, in combination with ribavirin (*2–4*).

## MATERIALS AND METHODS

The effect of antiviral therapy was retrospectively assessed on 131 patients with CHC. The use of particular regimens reflects the history of the development in search of the most effective method of treatment of this disease. Each patient first underwent an initial course of alpha-IFN treatment in dosages of 3 MU three times a week. Forty-eight patients were treated in this fashion for six months (group A) and 83 for 12 months (group B). Thirty-three patients underwent subsequent combination therapy with alpha-IFN and ribavirin, of which 17 had relapsed after the initial course of therapy (group C) and 16 had not responded to alpha-IFN in monotherapy (group D). Alpha-IFN was given in dosages of 3 MU three times a week during the course of combination therapy; ribavirin was given daily (1000 mg by patient weight to 75 kg and 1200 above 75 kg) in two daily doses.

Chronic HCV infection was detected in all patients by means of anti-HCV antibodies (second or third generation ELISA test) and confirmed by the presence of viral nucleic acid (HCV RNA) in serum by polymerase chain reaction (PCR).

The absolute majority of patients (125/131, 95 %) underwent liver biopsy before treatment. The remaining six patients could not undergo biopsy due to the risk of haemorrhage brought on by the fact that they suffered from haemophilia. Histological findings were classified into four groups for the sake of simplicity according to the grading and staging of the liver inflammatory process (chronic persistent hepatitis – CPH; chronic active hepatitis – CAH; advanced, fibrotic, chronic active hepatitis – CAH/LC; and liver cirrhosis – LC). There were only three cirrhotic patients in the group, all in the stage corresponding to the classification Child A.

For economic reasons, it was only possible to conduct HCV serotyping on 87 patients (66 %). The immunoassay Murex HCV Serotyping 1–6 Assay was used.

Likewise, it was possible that only some of the patients underwent a pre-treatment quantitative assay of viremia using the hybridization method. Again the reason was the large financial burden of this examination. Patients from group A could not be examined using this method before treatment, as at the time of their treatment this method was unavailable to us. The Quantiplex HCV RNA 2.0 Assay (bDNA) from the Chiron Corporation, USA, was used in all cases.

### Statistical Analysis of Data

The relative frequencies that occurred in disparate variants nearly covered the whole spectrum of possible values (0–100). The binomial estimates (p) in such extreme variants were then subjected to arcsine and square root transformation prior to any statistical testing ($p_{tr}$ = arcsine $\sqrt{p}$) that brought the underlying distribution to near normal levels. After statistical processing, all the binomial data were transformed back by sin function and expressed in original values (%) with correction for possible bias. Two sample estimates of age were based on an independent t-test. Differences with p values under 0.05 were considered significant.

## RESULTS

The basic characteristics of each group are shown in *Table 1.* In terms of average age, the groups A and B, and C and D were comparable. Men predominate in statistically significant numbers in groups B-D ($p<0.05$); in group A the gender balance is even.

Histologically, patients with CPH prevail in group A ($p<0.01$); the situation is analogous in groups C and D. It was not possible to resolve the distribution of CPH and CAH in group B (*Table 2*).

*Table 3* shows the HCV serotypes of patients from the individual groups. Type 1 unambiguously predominated in our groups. It was present, either independently or in combination with another type, and where it was possible to determine the serotype using this method, in 28 out of 32 patients from group A (88 %), 39 out of 43 from group B (90 %), 13 out of 14 from group C (92 %), and all 13 from group D (100 %). Other serotypes were exhibited only exceptionally (six of type 2, three of type 3), and it was, therefore, not possible to compare whether the treatment results were better with these patients than with those infected with type 1. It was not possible to determine the serotype of 14 patients using this method.

Pretreatment viremia could only be determined among some of the patients in group B (43/83), C (15/17), and D (15/16). The threshold between low and high viremia is given in the literature as a value of two million copies of the virus per millilitre (using quantitative PCR). This corresponds to a value of 2 MEq/ml in the hybridization method that we used. From the standpoint of viremia, group D demonstrates a significant predominance of high viremia, and in this sense it differs in a statistically significant way from group C ($p<0.05$) *(Table 4).*

*Table 5* shows the treatment results of patients from groups A-D. It has become conventional to define response to treatment as normalization of alanine transaminase (ALT) – *biochemical response*, and the development of negative serum HCV RNA – *virological response*. *End-of-treatment response* is always better than *sustained response*, which is defined as both a biochemical and a virological response 24 weeks after ending the therapy. End-of-treatment virological response (ETVR) was achieved with 19 % of patients from group A, 36 % from group B, 59 % from group C, and 13 % from group D. Serum HCV RNA was also negative 24 weeks after the treatment (sustained virological response – SVR) in 6 %, 19 %,

*Table 1*
Basic group characteristics

| | | Group A | | Group B | | Group C | | Group D | |
|---|---|---|---|---|---|---|---|---|---|
| Number of patients | | 48 | | 83 | | 17 | | 16 | |
| Men | % | 27 | 56.3 | 51 | 61.4 | 11 | 64.7 | 13 | 81.25 |
| Women | % | 21 | 43.7 | 32 | 38.6 | 6 | 35.3 | 3 | 18.75 |
| Average age | | 49 | | 40 | | 44 | | 43 | |
| Age range | | 21–77 | | 24–74 | | 25–77 | | 24–69 | |

*Table 2*
Baseline histological findings

| | Group A | | Group B | | Group C | | Group D | |
|---|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % | No. | % |
| CPH | 25 | 52.1 | 37 | 48.0 | 10 | 62.5 | 9 | 56.25 |
| CAH | 11 | 22.9 | 32 | 41.6 | 4 | 25.0 | 4 | 25.0 |
| CAH/LC | 11 | 22.9 | 6 | 7.8 | 2 | 12.5 | 3 | 18.75 |
| LC | 1 | 2.1 | 2 | 2.6 | 0 | 0.0 | 0 | 0.0 |
| Total | 48 | 100 | 77 | 100 | 16 | 100 | 16 | 100 |
| Not conducted | 0 | | 6 | | 1 | | 0 | |

For abbreviations see the list on the front page.

*Table 3*
The results of HCV serotyping

| | Group A | | Group B | | Group C | | Group D | |
|---|---|---|---|---|---|---|---|---|
| Serotype | No. | % | No. | % | No. | % | No. | % |
| 1 | 26 | 78.8 | 35 | 64.8 | 12 | 75.0 | 13 | 100 |
| *1+2* | 1 | 3.0 | 2 | 3.7 | 1 | 6.25 | 0 | 0.0 |
| *1+5* | 1 | 3.0 | 2 | 3.7 | 0 | 0.0 | 0 | 0.0 |
| *2* | 4 | 12.2 | 1 | 1.9 | 1 | 6.25 | 0 | 0.0 |
| *3* | 0 | 0.0 | 3 | 5.6 | 0 | 0.0 | 0 | 0.0 |
| *Not determined* | 1 | 3.0 | 11 | 20.3 | 2 | 12.5 | 0 | 0.0 |
| *Total* | 33 | 100 | 54 | 100 | 16 | 100 | 13 | 100 |
| Not conducted | 15 | | 29 | | 1 | | 3 | |

*Table 4*
Quantitative determination of viremia

| | Group B | | Group C | | Group D | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| Viremia | | | | | | |
| Low (≤2 MEq/ml) | 18 | 41.9 | 7 | 53.3 | 3 | 20.0 |
| High (>2 MEq/ml) | 25 | 58.1 | 8 | 46.7 | 12 | 80.0 |
| Total | 43 | 100 | 15 | 100 | 15 | 100 |

*Table 5*
The results of therapy

| | Group A (N=48) | | Group B (N=83) | | Group C (N=17) | | Group D (N=16) | |
|---|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % | No. | % |
| ETVR | 9 | 18.8 | 30 | 36.1 | 10 | 58.8 | 2 | 12.5 |
| SVR | 3 | 6.3 | 16 | 19.3 | 5 | 29.4 | 1 | 6.3 |
| ETBR | 21 | 43.8 | 40 | 48.2 | 16 | 94.1 | 8 | 50.0 |
| SBR | 5 | 10.4 | 14 | 16.9 | 6 | 35.3 | 1 | 6.3 |

For abbreviations see the list on the front page.

*Table 6*
Dependence of response to treatment on pretreatment viremia in group B

| | Low viremia | | High viremia | |
|---|---|---|---|---|
| | No. | % | No. | % |
| ETVR | 11/18 | 61.1 | 7/25 | 28.0 |
| SVR | 3/18 | 16.7 | 2/25 | 8.0 |
| ETBR | 12/18 | 66.7 | 12/25 | 48.0 |
| SBR | 1/18 | 5.6 | 2/25 | 8.0 |

For abbreviations see the list on the front page.

29 %, and 6 % of patients from groups A-D. In terms of normalization of ALT levels, groups A-D achieved end-of-treatment biochemical response (ETBR) with 43 %, 48 %, 94 % and 50 %; with 10 %, 17 %, 35 % and 6 % of those treated showing sustained biochemical response (SBR). Sustained eradication of HCV RNA from the serum is generally considered to be the most important indicator of successful treatment. This was achieved more often in a statistically significant sense among patients from group C than from group D ($p<0.05$); there were no significant differences between groups A and B. In terms of sustained biochemical response, the results were the same – significantly better results in group C than in group D ($p<0.05$); no significant differences between groups A and B.

*Table 6* shows the dependence of response to treatment on pretreatment viremia in group B. Unfortunately, the number of patients for whom it was possible to establish this meaningful predictive factor of successful treatment was relatively small, which distorts the results and makes their interpretation difficult. 61 % of the patients from group B with low pretreatment viremia ($\leq$ 2 MEq/ml) showed an ETVR, which was significantly higher than that of the 28 % of patients with high viremia ($p<0.05$). SVR was, however, without significant difference (17 % versus 18 %).

Alpha-IFN treatment is usually accompanied by a host of adverse events, which arise from the high biological activity of this medication. The "flu-like syndrome" (fever, headache, muscle ache, joint pain, tiredness) was often registered among our patient groups after initial doses of alpha-IFN. In an absolute majority of the cases, tolerance to treatment gradually improved. Less common complaints were an increase in hair loss and digestive problems (loss of appetite, diarrhoea or constipation). The only one serious adverse event of alpha-IFN treatment in monotherapy was a case of hyperthyroidism in a patient who had no previous history of thyroid problems. After discontinuation of alpha-IFN and medication with carbimazol, the condition rapidly improved.

Administration of ribavirin is regularly accompanied by haemolytic anaemia, which is connected with the danger of a manifestation of cardiac disease, specifically ischemic heart disease. One patient in group C (a 74-year-old woman) saw her haemoglobin level fall after five months of treatment to 88g/l (pretreatment level: 120g/l), which was associated with decompensation of ischemic heart disease with breathlessness, swelling and hydrothorax. Both medications were discontinued and the patient was compensated through the use of cardiotonics and diuretics. It is interesting to note that, even given the age of the patient, this unwanted side effect and the advanced stage of liver inflammation (CAH/LC), sustained elimination of HCV RNA from the serum and normalization of ALT occurred.

## DISCUSSION

Until recently, the procedure used in the treatment of CHC assumed an initial treatment with alpha-IFN with a subsequent course of combination therapy for

patients not evidencing a sustained cure. The results of large-scale, randomized, placebo-controlled clinical studies published at the end of 1998 showed, however, that combination therapy is much more effective even among untreated patients, and thus that primary monotherapy using alpha-IFN was superfluous and uneconomical. A total of 1,744 European and American patients who had not previously been treated with alpha-IFN were studied (*5,6*). They were treated with either alpha-IFN alone or with alpha-IFN and ribavirin. In both cases, the treatment period was six or twelve months. The dosages used were the same as those in our study. Sustained virological response was achieved in only 6 % and 12 % of patients treated with alpha-IFN alone in the course of six or twelve months respectively. Conversely, combination therapy leads to the same result in 33 % and 41 % of cases respectively. A biochemical response was seen in 11 %, 20 %, 36 %, and 44 % of patients treated with the above-mentioned therapeutic programme. Thus, similar results were achieved as those that we had reached with our patients in groups A and B. On the basis of the results of these large-scale studies, independent predictive factors for the successful treatment of patients with chronic hepatitis C using IFN in monotherapy or in combination with ribavirin were established. There are especially infection with genotypes non-1, low baseline viremia, and absence of LC or bridging fibrosis.

In another multicentre study (*7*), a total of 345 patients who had previously relapsed after initial treatment with alpha-IFN were treated either with alpha-IFN in monotherapy or in combination with ribavirin. The treatment period in both cases was six months. Sustained virological results were achieved in only 5 % of the patients treated with alpha-IFN alone and almost half (49 %) of those treated in combination with ribavirin (similarly also normalization of ALT at 5 % and 47 % respectively). Thus, even better results than were achieved in the above-mentioned studies with previously untreated patients. If we compare these results with those of our patients from group C, we can see that we were not so successful in our treatment, even though our patients were treated for whole 12 months. The main reason for this difference is probably the fact that, in the study cited, only 57 % of the patients in the combination group were infected with genotype 1 (whereas in our study, 91 % of those for whom it was possible to establish the genotype were so infected).

The results of the above-mentioned international studies became, above all, a reference basis coming out of the International Consensus Conference, which was organized by the European Association for the Study of the Liver in Paris in February of 1999. According to these recommendations, all patients suffering from chronic HCV should be treated with alpha-IFN in combination with ribavirin, whether they have been previously treated with alpha-IFN or have relapsed after previous treatment. The only exception is patients for whom the administration of ribavirin is contraindicated. In these cases it is necessary to administer alpha-IFN in monotherapy, probably in higher dosages than 3 MU three times weekly. The

duration of the combination therapy depends on the genotype of the virus and initial viremia. A six-month treatment is sufficient for patients infected with genotypes 2 and 3 without regard to initial viremia. The same length of treatment is also recommended for patients with genotype 1 and low initial viremia (*1*).

The course to be taken with patients whose initial alpha-IFN therapy failed is much less clear. Even combination therapy with ribavirin is not effective in the majority of these patients. The success rate of combination therapy with these patients is given to be under 10 % (*8*). One patient in 14 from our group D saw a sustained virological response (7 %). A strict individual approach is necessary with these patients. Above all, daily administration of alpha-IFN during the first 1–2 months comes into consideration. This induction phase is followed by a subsequent maintenance phase at three times weekly and the administration of pegylated IFN. Both courses of action hinder the fall in plasmatic concentration of alpha-IFN to a level below that necessary for the suppression of reproduction of the virus (which is achieved by a standard dosage of three times weekly). This lowers the probability of the emergence of resistant mutant strains. Triple combination therapy with alpha-IFN, ribavirin and amantadine and consensus IFN treatment present other possibilities. As yet, there is little data that would enable an unambiguous recommendation of these treatment approaches.

Even at the turn of the millennium, the treatment of chronic HCV poses a serious problem for modern medicine. Much has already been achieved to improve the prognosis for those suffering from this insidious and dangerous disease, but many more problems still await a solution. Until yet more effective means to a complete cure of this disease or at least a substantial slowing of its progress have been found, there will always be a large number of patients who will reach the terminal stages of the illness, where their only hope will be a liver transplant. Huge sums have been and are being invested on a world scale in the fight against HCV. Thus perhaps the hope of a fundamental turn in the success of our treatment efforts is justified. Until a vaccine against HCV is created, however, it is impossible to foresee this infection coming under our long-term control. Much attention has been given to this problem as well. For the time being, however, a successful conclusion of our research remains out of sight, above all given the abnormal genetic variability of HCV.

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# MONOTERAPIE ALFA-INTERFERONEM A KOMBINOVANÁ TERAPIE ALFA-INTERFERONEM A RIBAVIRINEM U NEMOCNÝCH S CHRONICKOU HEPATITIDOU C


## Souhrn

Srovnávali jsme účinnost 6 a 12 měsíců léčby alfa-interferonem v monoterapii u dosud neléčených pacientů. Porovnali jsme efekt kombinované léčby alfa-interferonem a ribavirinem u pacientů, kteří relabovali po původní monoterapii alfa-interferonem, a u nemocných, kteří na původní léčbu vůbec neodpověděli. Retrospektivně byl posouzen efekt antivirové terapie u 131 dosud neléčených pacientů s chronickou virovou hepatitidou C. Všichni dostávali alfa-interferon v dávce 3 MU třikrát týdně, přičemž 48 z nich šest měsíců (soubor A) a 83 dvanáct měsíců (soubor B). Následnou kombinovanou terapii alfa-interferonem (ve stejné dávce) a ribavirinem (1,0 nebo 1,2 gramů denně) absolvovalo 17 nemocných relabujících po předchozí monoterapii alfa-interferonem (soubor C) a 16 pacientů, kteří na původní léčbu vůbec neodpověděli (soubor D). Setrvalé virologické odpovědi (negativizace nukleové kyseliny viru hepatitidy C v séru po 24 týdnech od skončení léčby) bylo dosaženo u 6 %, 19 %, 29 % a 6 % nemocných ze souborů A-D. Výsledky kombinované léčby byly u relabujících významně lepší ($p<0,05$) než u neodpovídajících. U dosud neléčených pacientů nebyly nalezeny statistické významné rozdíly v závislosti na délce léčby (6 nebo 12 měsíců). U 61 % nemocných ze souboru B s nízkou vstupní virémií ($\leq$ 2 MEq/ml) došlo k virologické odpovědi v době ukončení léčby, což bylo významně častěji než u 28 % pacientů s vysokou virémií ($p<0,05$). Setrvalá virologická odpověď však byla bez významných rozdílů (17 % versus 8 %). Závislost odpovědi na sérotypu viru nemohla být hodnocena, protože naprosto převládal typ 1 (88 % v A, 90 % v B, 92 % v C a 100 % v D).

U dosud neléčených pacientů nebyly nalezeny statistické významné rozdíly v závislosti na délce léčby (6 nebo 12 měsíců). Výsledky kombinované léčby byly u relabujících významně lepší ($p<0,05$) než u neodpovídajících.


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