REVIEW

Treatment of chronic hepatitis C patients with combination of alpha-interferon and ribavirin, consensus and pegylated interferons

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Abstract

Hepatitis C is a major health problem. In recent years, the treatment of choice is alpha-interferon in combination with ribavirin. For patients with failure of this treatment the therapy with consensus or pegylated interferons, in monotherapy or in combination with ribavirin, present other possibilities. We can expect the development more potent antiviral drugs or immune modulators for patients, which are primary resistant to alpha-interferon. (*Tab. 3, Ref. 31).*

Key words: chronic hepatitis C, alpha-interferon, ribavirin, consensus interferon, pegylated interferon.

Hepatitis C is a major health problem. The global prevalence of chronic hepatitis C (CHC) is estimated to average 3 %: there are some 150 million chronic HCV carriers all over the world, of whom an estimated 4 million are in USA and 5 million in Western Europe. 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 exceptional importance of HCV infection (EASL International Consensus Conference on Hepatitis C — Consensus Statement, 1999).

Alpha-interferon

The concept of interferon (IFN) is historically linked with viral interference — a phenomenon by which cells culture or animal infected by certain virus is resistant to infection by another virus inoculated at the same time or immediately after the first. The possibility that the status of resistance might be mediated by a soluble factor released by infected cells was deduced from the experiments of Nagano and Kojima in 1950s. However, there is no doubt that IFN, as a soluble mediator of viral interference, was effectively discovered by Isaacs and Lindenmann in 1957 and these authors used the term interferon for the first time. Interferons (IFNs) have antiviral, antiproliferative and immunomodulatory effects. The recent classification of IFNs is based on the structure of their genes. There are four types of human IFNs — alpha, beta, gamma, and omega (Kontsek and Kontseková, 1998).

Therapy of chronic hepatitis C with alpha-interferon

The first attempts at treating CHC come from the period when the agent of the disease was unknown and was temporarily designated as post-transfusion non-A, non-B hepatitis. Since that the treatment of choice has been alpha-IFN in monotherapy, and, in recent years, in combination with ribavirin (Schalm et al., 1996, 1997; Reichard et al., 1998).

It has become conventional to define response to treatment as normalization of alanine transaminase (ALT) — biochemical response, the development of negative viral nucleic acid (HCV RNA) — virological response, and significant improvement of liver inflammation evaluated by different scoring systems — by Knodell, Ishak or METAVIR classification — histological response. Virological response is the best correlate of cleared infection in response to treatment. End-of-treatment response is always better than sustained response, which is usually defined as both a biochemical and virological responses 6 months after ending the therapy. Patients with sustained response are called responders; relapsers are those with initial response and then with reappearance of HCV RNA in serum and ALT activity after ending the therapy; non-

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responders have not cleared HCV RNA and normalized ALT activity during alpha-IFN therapy. Breakthrough phenomenon is characterized by initial disappearance of HCV RNA from serum and its reappearance even before the end of alpha-IFN therapy. Naive patients are persons still untreated with alpha-IFN.

Combination therapy with alpha-interferon and ribavirin

Ribavirin is a rapidly absorbed, oral, synthetic guanosine nucleoside analogue that is active against a range of RNA and DNA viruses. It has been used as monotherapy for hepatitis C virus infection, leading to decrease serum transaminase levels and improved histology, but it has no effect on HCV RNA levels. Ribavirin has also been used in combination with alpha-IFN, producing increased sustained virological response rates by unknown mechanism of action, probably by immune modulation. The administration of alpha-IFN three times per week is associated with a rebound of viral replication at day 2. The rebound appears to be prevented by the adjunction of ribavirin in most cases. Daily alpha-IFN administrations (Gretch, 1998), as well as weekly administration of pegylated IFN, induce a biphasic decrease of viral load. The first, rapid phase at day 1 is related to direct non-specific inhibition of HCV replication. The second, slower phase starts at day 2 and leads to viral clearance within a few weeks to months in most cases. It is likely related to cell death. Induction therapy can be improved by the development of drugs targeting virus production, de novo infection of hepatocytes and/or infected cell death. Maintenance therapy is necessary to prevent relapse in the patients who cleared HCV replication during induction therapy (Neumann et al., 1998; Zeuzem et al., 1998; Pawlotsky et al., 2000).

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 those patients not showing 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 (Poynard et al., 1998) and American patients (McHutchinson et al., 1998) who had not previously been treated with alpha-IFN were studied. They were treated with either alpha-IFN alone (3 MU three times weekly) or with alpha-IFN and ribavirin (1.0 or 1.2 g daily). In both cases, the treatment period was six or twelve months. 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 led to this 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 scheme. On the basis of the results of these large-scale studies, independent predictive factors for the successful treatment of patients with CHC using alpha-IFN in monotherapy or in combination with ribavirin were established. These are given in table 1.

In another multicenter study (Davis, 1998) 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 those 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 were achieved than in the above-mentioned studies with previously untreated patients.

The results of the above-mentioned international studies became, best of all, the basis for reference coming out of the International Consensus Conference, which was organized by the European Association for the Study of the Liver in Paris in February 1999. According to these recommendations, all patients suffering from CHC should be treated with alpha-IFN in combination with ribavirin, whether they have been previously untreated with alpha-IFN or have relapsed after previous treatment. The only exception are those for whom the administration of ribavirin is contraindicated. In these cases it is necessary to administer alpha-IFN in monotherapy, probably in higher doses than 3 MU three times weekly. The duration of combination therapy depends on the genotype of the virus and initial viremia (Table 2.). Given the relatively low efficacy and side effects of the current treatment of hepatitis C, some patients with hepatitis C virus infection are not suitable candidates for therapy. Patients who should not be treated are in table 3 (EASL International Consensus Conference on Hepatitis C – Consensus Statement, 1999).

Pegylated Interferon

Polyethylene glycol (PEG) is a water-soluble, nontoxic polymer that can be covalently linked to different proteins. Pegylation increases protein half-life by reducing renal clearance and proteo-

Tab. 1. Independent Favorable Predictive Factors for IFN Treatment in Monotherapy and in Combination with Ribavirin (McHutchinson et al., 1998; Poynard et al., 1998).

Genotype other than 1
Absence of cirrhosis or portal fibrosis
Low pretreatment viremia (≤2 million copies/ml)
Female gender
Age ≤40 years

Tab. 2. Recommendation of EASL for duration of combination treatment (EASL International Consensus Conference on Hepatitis C – Consensus Statement, 1999).

	Genotype 1- Low viremia	Genotype 1- High viremia	Genotype 2,3- Low viremia	Genotype 2,3- High viremia
Naive patient	24 weeks	48 weeks	24 weeks	24 weeks
Relapser	48 weeks	48 weeks	24 weeks	48 weeks

Tab. 3. Patients which should not be treated (EASL International Consensus Conference on Hepatitis C – Consensus Statement, 1999).

Heavy alcoholics
Active intravenous drug users
Patients with decompensated cirrhosis
Patients with histologically mild disease
Patients with contraindications of IFN and/or ribavirin

lysis. Pegylation leads to less antigenicity, increased solubility, and thermal as well as chemical stability of the base protein. Pegylated interferon (PEG-IFN) has an increased plasma half-life (40 hours versus 4 hours) and thus it can be administered only once a week. We suppose the use of PEG-IFN especially in the treatment of CHC, as its plasma level is permanently high enough for suppression of viral replication.

Two PEG-IFNs are currently being studied. The linear 12 kDa pegylated IFN, PEG-IFN alpha-2b, was found to have maximal serum concentrations 8 to 12 hours after administration and sustained maximal plasma concentrations 48 to 72 hours after administration. Its half-life is 30.7 hours and it is eliminated predominantly via kidneys.

PEG-IFN alpha-2a has a branched-chain 40 kDa PEG. It is metabolized above all by liver. Substantial concentrations of this IFN are achieved within 3 to 8 hours after administration, and maximum serum concentrations were reached at approximately 80 hours. Renal clearance was 100-fold slower than that seen with standard alpha-IFN. Therapeutic levels of PEG-IFN alpha-2a are maintained for prolonged periods of time, up to 168 hours (Wright, 2000).

The results of three large international multicenter randomized studies were published till the end of the year 2000. These studies compared the efficacy of PEG-IFNs with standard IFNs.

In the first study (Zeuzem et al., 2000) were randomized 531 naive patients with CHC to receive either 180 g of PEG-IFN alpha-2a once per week for 48 weeks or 6 MU of standard IFN alpha-2a three times per week for 12 weeks, followed by 3 MU three times per week for 36 weeks. PEG-IFN was associated with a higher rate of sustained virological response than was IFN alpha-2a (39 % versus 28 %, p=0.001).

In the second study (Trépo et al., 2000) 1219 chronic hepatitis C patients were treated with one of three doses of PEG-IFN alpha-2b (0.5; 1.0; 1.5 g/kg once weekly) or standard IFN alpha-2b (3 MU three times weekly). Sustained virological response was achieved in 12 % patients treated by IFN alpha-2b and in 18 % (p=0.042 vs. IFN alpha-2b), 25 % (p=0.001), and 23 % (p=0.001) in the different doses groups of PEG-IFNs. All three PEG-IFNs doses were superior to standard IFN, while keeping the same safety profile.

In the last study (Heathcote et al., 2000) were randomly assigned 271 patients with cirrhosis or bridging necrosis to receive 3 MU of alpha-IFN 2a three times weekly; 90 g of PEG-IFN alpha-2a once a week; or 180 g of PEG-IFN alpha-2a once a week for 48 weeks. Sustained virological response was achieved in 8 %, 15 %, and 30 % patients treated with therapeutic regimens mentioned above (p=0.001 for the comparison between 180 g of PEG-IFN alpha-2a and alpha-IFN 2a).

In all of these studies PEG-IFN and standard IFN were similarly tolerated.

Preliminary data suggest that the efficacy of PEG-IFN may be further enhanced by the addition of ribavirin to the treatment regimen. The final results of a small, pilot, study were already presented (Sulkowski and Reindollar, 1999). Even though, there were only 20 naive patients and 80 % with genotype 1, the sustained virological response 24 weeks after completing 48 weeks of combination therapy (180 g of PEG-IFN alpha-2a once weekly and 1.0 or 1.2 g of ribavirin daily) was 38 %. The four patients with genotype 2 had 100 % sustained virological response 24 weeks after completing a 24-week duration of combination therapy.

The second study was an open-label, randomized, active control study, enrolling 72 patients. PEG-IFN alpha-2b was administered at 0.35 g/kg, 0.7 g/kg, or 1.4 g/kg weekly by a single injection. PEG-IFN was administered alone or in combination with ribavirin in doses mentioned above. The sustained virological response was higher in every group receiving combination therapy when compared with those receiving PEG-IFN alone. The response was highest in the group receiving the 1.4 g/kg dose (61 %), still excellent in 0.7 g/kg dose group (53 %), and lowest in 0.35 g/kg dose group (17 %).

In both of these studies the tolerance of therapy was similar to combination of standard IFN and ribavirin.

Consensus Interferon

Consensus interferon (CIFN) is a recombinant IFN, composed of the most frequently observed amino acid at each position of different types of alpha-IFNs. CIFN shares 89 % homology with alpha-IFNs and 30 % homology with beta-IFNs. The in vitro antiviral and antiproliferative activity of CIFN was found to be higher than the ones observed with standard alpha-IFN. For instance, the antiviral activity of CIFN, using VSV or HSV infected human cells lines, appeared to be even up to tenfold higher than for IFN alpha-2a a 2b. The higher specific activity of CIFN may be explained by the tenfold stronger binding to the IFN receptors on cells surface (Ozes et al., 1992; Blatt et al., 1996).

The optimal dose regimen is still under evaluation. In the first study (Tong et al., 1997) 704 nad've chronic hepatitis C patients were randomized for 24-week treatment with IFN alpha-2b (3 MU three times weekly) or CIFN (9 g three times weekly). The rate of sustained virological response in both groups of patients was comparable (11 % and 12 %) but CIFN was significantly more efficient in so called problematic patients — with genotype 1 (8 % vs. 4 %, $p<0.05$) or high pretreatment viremia (7 % vs. 0 %, $p<0.05$).

The second study (Heathcote et al., 1998) evaluated the efficacy of re-treatment with a higher dose of CIFN (15 g three times weekly) for a period of 24 or 48 weeks in 337 patients who either did not respond to, or had relapsed after, prior therapy with CIFN (3 or 9 g three times weekly) or IFN alpha-2b (3 MU three times weekly). For relapsers, the sustained virological response rate was 58 % (24 weeks) and 28 % (24 weeks, p=0.024). CIFN 15 g monotherapy of previous relapsers with difficult to treat genotype 1 and high viral load was found to be as effective as combination therapy with IFN alpha-2b and ribavirin (27 % vs. 25 % of sustained virological response) (Davis et al., 1998) and superior to re-treatment with standard IFN alpha-2b monotherapy (0-4 %) (Andreone et al., 1999). The sustained virological response rate among prior non-responders was 13 % (48 weeks) and 5 % (24 weeks). The administration of higher dose of CIFN (15 g) was well tolerated and was not associated with an increase of the incidence of side effects. This data demonstrate that re-treatment with 15 g CIF is safe and effective therapy for previous relapsers and non-responders to IFN monotherapy.

Therapeutic Innovation in Chronic Hepatitis C Patients

There are some biological similarities between HCV and HIV, which strongly support the use of combination therapy in HCV

infection. HCV is produced in large amounts by infected hepatocytes. Newly synthesized virions de novo infect new hepatocytes, whereas infected hepatocytes are progressively cleared by cell death. The vast majority of the produced virions are released in the general circulation, where they are continuously degraded. At the chronic stage of infection, this system is at a steady state, characterized by half-lives of free virions of 2.7 hour, and daily production/clearance rates of the order of 10^{12} virions/day. The current standard of therapy of HIV infection is so called HAART (highly active antiretroviral therapy), which consists of combination of minimum three antiretroviral drugs. At present, we have alpha-IFN and ribavirin for therapy of HCV infection and maybe one of the possibilities how to improve the efficacy of this therapy is to find the third potent drug for combination treatment. The most promising candidates for the role of the third drug are now amantadine and thymosin-alpha 1 (Smith et al., 1997; Rasi et al., 1996; Moscarella et al., 1998).

Studies are beginning to focus on inhibitors of HCV replicative enzymes (anti-helicase or specific antiprotease), cytokines and cytokine modulators, immune modulators, and non-specific cytoprotective agents. Interleukin (IL)-10, a cytokine that down-regulates proinflammatory response and modulates hepatic fibrogenesis, was recently reported to normalize serum ALT, to improve histology, and to reduce liver fibrosis in patients receiving treatment. Also of current interest are synthetic stabilized ribozymes that are designed to cleave specific RNA sequences. Hammerhead ribozymes have been developed to target conserved sites in the untranslated regions of HCV RNA. Early investigation of these ribozymes has demonstrated their potential in preclinical studies. Antisense oligonucleotides targeted against the ribosomal-binding site of the 5'non-translated region of the HCV genome are being investigated (Zeuzem et al., 1997; Pardo et al., 1995; Brotons et al., 1997; Horák and Stříteský, 1999).

Conclusion

Even at the turn of the millennium, the treatment of CHC 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 even more effective means to a complete cure of this disease or at least the substantial slowing of its progress are 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 discovered, 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 because of the abnormal genetic variability of HCV.

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Abstrakt

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Léčba chronické hepatitidy C kombinací alfa-interferonu a ribavirinu, konsenzuálním a pegylovaným interferonem.
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Virová hepatitida C představuje závažný zdravotnický problém. Lékem volby je nyní kombinace alfa interferonu a ribavirinu. Pro pacienty, u kterých tato léčba selže, představují další možnost pegylovaný, či konsenzuální interferon buď v monoterapii, nebo lépe v kombinaci s ribavirinem. V budoucnosti lze předpokládat, že budou zavedena do praxe nová účinnější virostatika a imunomodulátory. Jejich význam bude pravděpodobně největší u nemocných infikovaných virem hepatitidy C, který je na alfa-interferon primárně rezistentní. *(Tab. 3, lit. 31.)*
Klíčová slova: chronická hepatitida C, alfa-interferon, ribavirin, konsenzuální interferon, pegylovaný interferon.

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