

Pegylated Interferon and Ribavirin: Evidence for their Role in Hepatitis C

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Hepatitis C is a major cause of liver related morbidity and mortality. The virus, a member of the family *Flaviviridae*, is a single stranded RNA of which several genotypes are known. The existence of various genotypes is more than a curiosity for molecular biologists: type 1 infected patients being less responsive to current treatment¹. Viral genotype distribution varies in different continents and countries. In Bahrain we found that Type 1b was predominant being detected in 36.3% while Type 3 was found in 18.1%².

The virus, similarly to what is described for hepatitis B virus, is transmitted through blood, sexual contact, *in utero* (although at a lesser extent than HBV) and during delivery³. Dialysis patients are at a higher risk. In many cases, due to the long time interval between the exposure and the appearance of symptoms it is difficult to trace the source of the infection. Laboratory diagnosis is made by antibody detection and uncovering of the viral genome by polymerase chain reaction. The presence of the virus *per se* does not indicate active or current disease. It is possible that biochemical tests of liver function are still normal (in some patients they can remain normal for many years despite viral presence) but it has also been shown that histological liver abnormalities can be present with normal biochemical parameters. Anyway, tendency to chronicity is reported higher than 80%. Of special interest is the association of HCV infection with cryoglobulinemia⁴ and lymphomas both in adults and in children^{5,6}.

Thus, to establish a firm diagnosis of HCV infection with liver damage it is recommended to perform, together with virological assays, liver functions test (ALT determination) at least three times within a period of six months. If they are persistently altered in presence of HCV RNA in the blood, therapy can be considered. If therapy is decided it is suggested to take a liver biopsy, to determine the viral load and viral genotype.

Viral load at time 0 is an important parameter to assess at week 24 the response of the patient to therapy, viral genotype is important for the prognosis: patients with type 1 have less than 10 % chances to have a sustained virological and biochemical response. Patients infected with types 2 and 3 can be treated, according to some, for a shorter course of 24 weeks¹.

Therapy was based until one year ago on interferon 3MU administered subcutaneously three times a week for 48 weeks. More recently Ribavirin was added.

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Interferon provided a response rate of 48%, but the relapse rate was high, leaving a therapeutic efficacy on the long term limited to 10% of treated cases. The addition of ribavirin increased the response rate to *circa* 40%. When data for type 2 and 3 were analyzed separately the response rate went up to 66%. Beside the genotype, other factors associated with better response were: age less than 40, female sex, HCV viral load less than 2million copies /ml and little hepatic fibrosis.

Thus, INF plus ribavirin became in the late 90s the standard treatment for HCV infection. However several limitations were there, the most important being the need for frequent injections for a long period of time associated with toxic effects, all contributing to make patient compliance more difficult. In 2000 and in 2001, new formulations of IFN⁷⁻⁹, Pegylated IFN (PEG-IFN) were approved by FDA. Their properties will be discussed here with the clinical available evidence of their effectiveness in selected clinical scenarios.

Data sources. Studies were identified by searching MEDLINE, Cochrane Database for Systematic Review (CDSR) ACP journal club, Database of Abstracts of Reviews of Effectiveness (DARE) and Cochrane Register of Controlled Trials CCTR).

Study selection. The reviewer went through the databases searching for “pegylated interferon” without any limitation of time and language. By doing this, 135 papers were selected. Out of these, 116 were within the time limits applied (January 1st 2001- November 30th 2002). Only four articles fulfilled the criteria of being original studies^{9, 12-14}.

Pegylated interferons (PEGASYS[®], Peg-interferon alfa-2a, Hoffmann-La Roche; PEG-Intron[®] Peg-interferon alfa-2b, Schering)

PEGASYS[®], peg-interferon alfa-2a, is a covalent conjugate of recombinant alfa-2a interferon (approximate molecular weight [MW] 20,000 daltons) with a single branched bis-monomethoxy polyethylene glycol (PEG) chain. Peginterferon alfa-2b (PEG-Intron[®] powder for Injection, Schering, approved by FDA January 2001) is a covalent conjugate of recombinant alfa interferon with monomethoxy polyethylene glycol (PEG). Both are produced using recombinant DNA technology in which a cloned human leukocyte interferon gene is inserted into and expressed in *Escherichia coli*.

Each vial contains PEGASYS[®], 1.2 mL of solution to deliver 1.0 mL of drug. Subcutaneous (SC) administration delivers 180 µg of active product. PEG-Intron[®] (Interferon alfa-2b, MW 31,000 daltons) is supplied in 2 mL vials for subcutaneous use. Each vial contains 74 µg, 118.4 µg, 177.6 µg, or 222 µg of the drug, which when reconstituted with sterile water, provides the drug in concentrations of 50 µg/0.5 mL, 80 µg/0.5 mL, 120 µg/0.5 mL, and 150 µg/0.5 mL. The recommended dosage for monotherapy is 1 µg/kg/week.

Injections should be given preferably in the thigh, outer surface of the upper arm, or abdomen, and the injection sites should be rotated. The dose should be administered on the same day each week. Following reconstitution, the medication should be administered immediately, but may be stored in a refrigerator for up to 24 hours.

A Cochrane review¹⁰ demonstrated that ribavirin alone had no significant effect on virological response or histological appearance and only a transient effect on the biochemical parameters. Combination therapy with Interferon demonstrated in naïve patients superiority to IFN alone or ribavirin alone in respect to a sustained virological, biochemical response and improved histology, associated with increased occurrence of adverse effects.

FDA approved the combination on August, 8th, 2001 for the treatment of adults at least 18 years of age with chronic hepatitis C who have compensated liver disease and have not been previously treated with interferon alfa.

PEG-Intron[®], however, has been subsequently approved for use in combination with ribavirin. The oral formulation of ribavirin is now also available as a single agent (for use in conjunction with peginterferon alfa-2b), whereas, previously, it was supplied as a combination package. Ribavirin is genotoxic and mutagenic and should be considered a potential carcinogen; may cause birth defects and/or death of the unborn child. Extreme care must be taken to avoid pregnancy not only in female patients but very important in female partners of male patients. The use of ribavirin is contraindicated in patients with hemoglobinopathies (eg. sickle cell anemia). Ribavirin caused hemolytic anemia, which may result in a worsening of cardiac disease in 10% of patients treated with the combination regimen within 1 to 4 weeks of initiation of therapy.

Clinical pharmacology.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface and initiate a complex sequence of intracellular events (Fig 1).

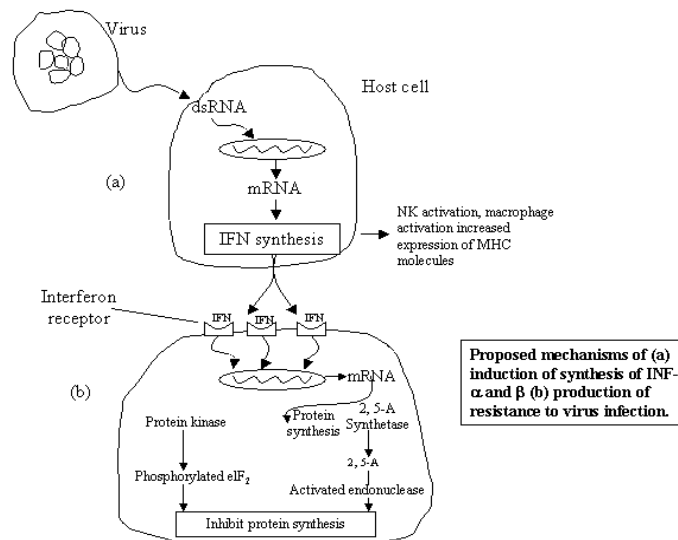


Figure 1. Antiviral mechanisms of interferons

These include the induction of certain enzymes, suppression of cell proliferation, immunomodulating activities such as enhancement of the phagocytic activity of macrophages and amplification of the specific cytotoxicity of lymphocytes for target

cells, and inhibition of virus replication in virus-infected cells. Interferon alfa up-regulates the Th1 T-helper cell subset in *in vitro* studies. The relevance of these findings from a clinical standpoint remains to be defined.

Pharmacodynamics: PEG-Intron[®] raises concentrations of effector proteins such as serum neopterin and 2'5' oligoadenylate synthetase, raises body temperature, and causes reversible decreases in leukocyte and platelet counts.

Pharmacokinetics: Following a single subcutaneous dose, the half-life ($t_{1/2}$ k_a) was 40 hours for PEG-IFN alfa-2b and 65 hours for alfa-2a (compared to the 5-8 of standard IFN). Maximal serum concentrations (C_{max}) occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours. Renal clearance of PEG-IFN alfa accounts for 30%, being reduced by one-half in patients with creatinine clearance <50 mL/minute. Ribavirin should not be used in patients whose creatinine clearance is less than 50 mL/minute.

Laboratory Tests

Before beginning INF and PEG-INF therapy, standard hematological and biochemical laboratory tests are recommended for all patients. After initiation of therapy, hematological tests should be performed at 2 weeks and biochemical tests should be performed at 4 weeks. Additional testing (Thyroid stimulating hormone) should be performed periodically during therapy. The following can be considered as a guideline to acceptable baseline values for initiation of treatment:

- Neutrophil count ≥ 1500 cells/mm³
- Platelet count $\geq 90,000$ cells/mm³ (as low as 75,000 cells/mm³ in patients with cirrhosis)
- Serum creatinine concentration <1.5 x upper limit of normal
- TSH and T₄ within reference range values

HCV RNA should be determined at 6 months following initiation of treatment. If high viral concentrations have persisted, it is recommended that peginterferon alfa-2b monotherapy or combination therapy be discontinued.

Clinical Studies

Clinical studies with Pegasys[®]. Superiority of PEG-IFN in respect to interferon was evident from two major studies published by Zeuzem S *et al*⁷ and by Heathcote EJ *et al*⁸ on the same issue of New England Journal of Medicine December 2000 (both sponsored by Hoffman–La Roche). Studies of similar design have been performed to assess the value of Pegasys[®] versus Interferon (Roferon[®]) using similar biochemical and virological markers to assess efficacy of therapy and sustained response.

Zeuzem`s conclusions were based on 531 patients randomly assigned to receive either PEG-IFN alfa-2a (180 µg once weekly) or 6 MU IFN alfa for 12 weeks followed by 3MU thrice a week, for 36weeks). They found a higher virological (39 percent vs 19 percent) and biochemical (45% vs 25%) response at 72 weeks in those receiving PEG-IFN, without an increase in frequency and severity adverse effects.

The second paper⁸ on which FDA approval was based included patients with cirrhosis and compares two different doses of PEG-IFN alfa-2a. They examined, in an intention-to-treat study, 271 patients divided in three groups: one to receive IFN 3MU

three times a week, PEG-IFN 90µg once a week and 180µg once a week for 48weeks plus the (now) standard 24 weeks of follow up after completion of therapy.

Results were optimal with the highest dose of PEG-IFN allowing a 54 rate of histological response (vs 31 and 44 % respectively), 34% of ALT normalization (vs 15% and 20%, respectively) and 30% HCV-RNA disappearance (vs 8% and 15%, respectively). One should remark that in this study the values of disappearance of HCV RNA and ALT normalization are remarkably low in comparison to other reports on IFN alfa activity. Again tolerability was similar. This contrasts with our review of the literature (Table 1) showing a variability of incidence of adverse effects with the three molecules.

Table 1. Selected Adverse Reactions Occurring in >1% of Patients in Hepatitis (%)

Body System / Adverse Events	PEGASYS 180 µg alfa-2a	ROFERON-A*	PEG intron alfa-2b
Gastrointestinal			
Nausea	23	30	43
Diarrhea	16	16	22
Abdominal pain	15	15	NF
Dry mouth	6	3	NF
General			
Fatigue	50	50	66
Pyrexia	36	41	46
Rigors	32	42	48
Injection-site reaction	22	18	75
Hematologic			
Neutropenia	21	8	26
Thrombocytopenia	5	2	NF
Metabolism and Nutrition			
Anorexia	17	17	32
Musculoskeletal, Connective Tissue and Bone			
Myalgia	37	38	56
Arthralgia	28	29	34
Neurological			
Headache	54	58	62
Insomnia	19	23	40
Dizziness	16	12	NF
Psychiatric			
Depression	18	19	31
Irritability	13	17	47
Anxiety	6	5	47
Skin and Subcutaneous Tissue			
Alopecia	23	30	36
Pruritus	12	8	29

*Either 3 MIU or 6/3 MIU of ROFERON-A[®]. NF = not found.

When the viral genotype is considered, response rates to PEG-IFN either alfa-2a or alfa-2b show average values of 23% among patients with viral genotype 1 and 48% in patients with other viral genotypes, indicating the resistance of this HCV type and the necessity for the clinician to ask for and for the microbiological laboratory to be able to provide the genotype of the infecting virus before starting of therapy.

Common findings of Pegasys[®] and Peg-Intron[®] studies were that the treatment response rates were similar in men and women and in non-Caucasians compared to

Caucasians. Response rates were lower in African-American and Hispanic patients and higher in Asians compared to Caucasians. However, the total number of non-Caucasian patients in all series was too small to rule out substantial differences. Matched pre- and post-treatment liver biopsies were obtained before and after treatment in 60%-70% of patients treated with both drugs and studies agreed in finding a modest reduction in inflammation compared to baseline that was similar in all treatment groups.

More recent data from Siebert U *et al*¹¹ indicates PEG-IFN plus ribavirin remained cost effective when compared with other treatment options and should be used as first line treatment without waiting for the response of the patients. This analysis was based on increase in life expectancy by 4.7 years plus increase in quality adjusted life years (QALY).

Adverse effects. Both pegylated interferons have common adverse effects. In the table the most relevant are presented and compared to those of interferon as derived by the several studies examined. **Flu-like** symptoms are among the most frequent adverse events. Some of these effects may be short-lived and some may be prevented by administering the drug at bedtime and by the use of acetaminophen. **Ophthalmologic** disorders may be induced or aggravated by alpha interferons. All patients should receive an eye examination at baseline, and patients with preexisting problems (*eg.* diabetic or hypertensive retinopathy) should receive periodic ophthalmologic exams during treatment. **Neuropsychiatric** adverse effects include relapse of drug addiction, drug overdose, aggressive behavior, psychoses, hallucinations, bipolar disorders and mania. **Bone marrow toxicity** may result in severe cytopenias often starting within the first 2 weeks of treatment. **Pulmonary disorders** such as dyspnea, pulmonary infiltrates, pneumonia, *bronchiolitis obliterans*, interstitial pneumonitis and sarcoidosis may be induced or aggravated by pegylated INFs as well as by alpha interferon therapy. Ulcerative **colitis and pancreatitis** have been observed in patients treated with alpha interferon. **Cardiovascular Disorders.** Hypertension, supraventricular arrhythmias, chest pain, and myocardial infarction have been observed. **Hypersensitivity and autoimmune disorders** include myositis, hepatitis ITP, psoriasis, rheumatoid arthritis, interstitial nephritis, thyroiditis and systemic lupus erythematosus. PEG-IFN aggravates **endocrine disorders** such as hypothyroidism and hyperthyroidism. Hyperglycemia and hypoglycemia have been observed.

Immunogenicity

Approximately 2% of patients treated with peg-interferon alfa-2b or interferon alfa-2a (PEGASYS[®]) developed low-titer neutralizing antibodies. Six percent (24/409) of patients treated with PEGASYS[®] developed binding antibodies as assessed by an ELISA assay. The percentage of patients whose test results were considered positive for antibodies is highly dependent on the sensitivity and specificity of the assays. The clinical and pathological significance of the appearance of neutralizing antibodies is unknown. No correlation of antibody development to clinical response or adverse events was observed. From our experience, biological assays are superior to immunological tests, and have the advantage of selecting only those patients producing antibodies capable of inhibiting the function of IFN. It was concluded that many antibodies detectable with standard immunological assays do not have any clinical consequence because they leave the activity of IFN unaffected.

Mother and child

Both Peg-interferons are classified in Pregnancy Category C, but the use in conjunction with ribavirin is in Category X. Both have not been studied for their teratogenic effect and are recommended for use in women of childbearing potential only when the patients are using effective contraception during therapy. Ribavirin may cause birth defects and/or death of the fetus, and it is contraindicated in women who are pregnant, as well as in men whose female partners are pregnant. The use of ribavirin should not be started until a report of a negative pregnancy test has been obtained just prior to the planned initiation of therapy. As appropriate, women should use at least two forms of contraception and have pregnancy tests monthly during therapy and for 6 months following discontinuation of therapy. It is not known whether PEGASYS[®] PEG-Intron[®] or their components are excreted in human milk.

The safety and effectiveness of PEGASYS[®] and of peginterferon alfa-2b, alone or in combination with ribavirin in children below the age of 18 years have not been established.

Critical appraisal of literature search

It is evident from the above description that the approval of PEG-IFN is based on a limited number of studies, carefully controlled and performed on a significant number of patients, adopting stringent criteria for assessing the results and all sponsored by pharmaceutical companies. Autonomous studies are extremely difficult to run and extremely costly. Thus, pharmaceutical companies are fulfilling an important role in supporting research, but on the other side, approval by FDA was done without independent studies being performed.

Our database inquiry (see above for details of the methodology) carried out without setting time limits or selected language showed 135 papers. Of those 116 fell within the time limits chosen (January 1st 2001- November 30th 2002). To our great surprise only 4 of the retrieved papers met the criteria for inclusion, the vast majority of them are review articles discussing and commenting a very limited number of original investigations.

A randomised, dose finding, multicenter, double blind trial comparing PEG-INF alfa-2b with INF alfa-2b was published by Lindsay KL *et al*¹² on behalf of the Hepatitis Interventional Therapy group. A significant number (1219) of adult patients not previously treated with interferon alfa, with elevated ALT, and compensated liver disease, detectable HCV RNA, and liver histology consistent with chronic hepatitis were enrolled after accurate selection, treated for 48 weeks and followed for additional 24 weeks after completion of therapy. They compared treatment with different dosages of PEG-Intron[®] (0.5, 1.0, or 1.5 µg/kg once weekly SC) to treatment with INTRON A (3 MU three times weekly SC). Patients were treated for 48 weeks and were followed for 6 months post-treatment. Seventy percent of all patients were infected with HCV genotype 1, and 74% of all patients had high (more than 2 million copies per mL of serum), baseline levels of HCV RNA. These parameters indicate a stringent selection of subjects being these two factors known to predict poor response to treatment.

Response was defined as undetectable HCV RNA by PCR and normalization of ALT at 24 weeks post-treatment. No significant difference was observed among the three

doses utilized (approximately 24% of 613 total patients evaluated) and all of them were proven more effective than interferon (INTRON A[®], 12% of 307 patients evaluated). Virological response was achieved in 25% of cases treated with 1.0 µg/kg vs 12% of cases treated with 3MIU of interferon TIW.

Patients with both viral genotype 1 and high serum levels of HCV RNA at baseline were less likely to respond to treatment with PEG-Intron[®]. Among patients with the two unfavorable prognostic variables, 8% (12/157) responded to PEG-Intron treatment and 2% (4/169) responded to INTRON A. Patients receiving PEG-Intron[®] with viral genotype 1 had a response rate of 14% (28/199) while patients with other viral genotypes had a 45% (43/96) response rate.

Ninety-six percent of the responders in the PEG-Intron[®] groups and 100% of responders in the INTRON A[®] group first cleared their viral RNA by week 24 of treatment.

PEG-IFN proved superior to IFN in regard to virologic response rates (loss of detectable viral RNA by PCR), the optimal dose being, in this study, 1.0µg/kg and in regard to decreased liver inflammation as documented by histological examination (24% versus 12% of treatment response – combined virologic and ALT normalization). No new adverse effects, compared to those known for INF were reported.

This well planned documented and conducted study demonstrates unequivocally the superiority of PEG-IFN in respect to IFN while preserving its safety profile.

The efficacy of PEG-IFN alfa-2a was addressed by Reddy *et al*¹³ in a randomised, dose finding (45, 90, 180, 270µg/kg) study enrolling a well characterized group similar to that described above, but much smaller in size (159 patients). Sustained virologic response was maximal with 180µg/kg, equal to 36% compared with 3% of INF). This excellent comparative performance can be attributed to the number of patients enrolled in the second study and to an exceptionally low response to INF in this group of patients.

No well-planned studies are available comparing the two PEG-IFNs currently available. However, it is the opinion of the Author that the therapeutical differences between the two molecules are minimal, if any. Obviously one major area of interest is the activity of PEG IFN in patients infected with HCV type 1. From the literature examined it seems that pegylation per se (as expected) does not extend the spectrum of activity to include type 1. The next question then is: Is PEG-IFN in association with ribavirin better than IFN plus ribavirin?

PEG-Intron[®] Monotherapy and PEG-Intron[®]/REBETOL Combination Therapy-Study

A randomized study by Manns MP⁹ and co-workers sponsored by Schering Plough was the basis for establishing both the activity of PEG-IFN alfa-2b and its better activity when combined with ribavirin. The response rate to the PEG-Intron 1.5µg/kg plus ribavirin 800 mg dose was higher than the response rate to Intron A/REBETOL[®]

(See Table 2). The response rate to PEG-Intron[®] 1.0/0.5µg/kg/REBETOL[®] was essentially the same as the response to INTRON A[®]/REBETOL[®].

Patients with viral genotype 1, regardless of viral load, had a lower response rate to PEG-Intron[®] (1.5 µg/kg)/REBETOL[®] compared to patients with other viral genotypes, but showed a significant improvement compared to IFN-Rebetol treatment. However, Patients with both poor prognostic factors (genotype 1 and high viral load) had a response rate of 30% (78/256) compared to a response rate of 29% (71/247) with INTRON A[®]/REBETOL[®].

Table 2. Rates of Response to Treatment

	PEG-Intron 1.5µg/kg REBETOL 800 mg	INTRON A 3 MIU REBETOL 1000/1200 mg
Overall ^{1,2} response	52% (264/511)	46% (231/505)
Genotype 1	41% (141/348)	33% (112/343)
Genotype 2-6	75%(123/163)	73% (119/162)

¹ Serum HCV RNA is measured with a research-based quantitative polymerase chain reaction assay by a central laboratory.

² Difference in overall treatment response (Peg-Intron[®]/REBETOL[®] vs. Intron A[®]/REBETOL[®]) is 6% with 95% confidence interval of (0.18, 11.63) adjusted for viral genotype and presence of cirrhosis at baseline.

One study published in the selected time period Buti M *et al*¹⁴ addressed this issue in 55 patients divided into two groups: one to receive 0.5µg /kg for 48 weeks +ribavirin (800 mg) and the other to receive a decreasing dosage of PEG IFN (from 3µg 1 week, 1.5µg for 3 weeks and 1.0µg for 44 weeks + ribavirin same dosage). The main finding of this study, suffering the limitation of small numbers and of a very empirical design, seems to be that the higher dose for the short initial time can provide a quicker and sustained virologic response. At the end of therapy HCV RNA became undetectable in 71% vs 61.5% of the patients receiving high dosage versus low dosage. Moreover the authors have carried out no follow up 24 weeks after therapy completion to demonstrate any difference in relapse after discontinuation of therapy. In addition, it should be noted that the dose of 0.5 µg/kg is not the appropriate comparison being below the one suggested by the manufacturer. From this superficially planned study one can conclude that presently there is no sound suggestion to explore bizarre therapeutical plans or to use higher initial doses of PEG-IFN.

Conclusions. From the published literature it appears evident that the percentage of patients responding to IFN alone is ca 15%. If IFN is combined with ribavirin (usually 1000-1200 mg) the sustained virologic response can increase up to 30%. It is clear that PEG-IFN is superior to IFN (25% vs 15% overall response), and that the association with ribavirin is able to increase 10-15 % the success rate in all patients including those infected with type 1. There is yet no evidence that higher doses can achieve better response on the short or long term.

Treatment of the Naïve Patient with Normal Alanine Aminotransferase (ALT) Levels

In consideration of the relevance of this topic we will report here the critical revision of the available literature without time limits including relevant selected presentations

of ongoing studies at international meetings. In our database search no published papers have been found. Only presentations at conferences are available for critical appraisal. Studies refer to INF alone or in combination with ribavirin.

Dealing with an HCV infected patients (HCV-RNA positive) presenting with normal liver enzymes is a common clinical experience. To date, there are no large trials that have answered the question of how best to treat this important group of patients. Currently, the treatment approach for this large group remains controversial. One of the questions frequently asked is whether liver biopsy should be performed in patients with normal ALT levels. It is suggested that patients with persistently normal ALT levels tend to have minimal disease on liver biopsy, although patients with cirrhosis secondary to hepatitis C may have normal liver tests. Therefore, a liver biopsy may be helpful in assessing the extent of liver damage in patients with normal ALT levels¹⁵.

The New York Normal ALT Study Group¹⁶ reported on the treatment of patients with normal ALT (defined as having at least 2 normal ALT values drawn at least 3 months apart) using 2 different doses of interferon alfa-2b with ribavirin. Following liver biopsy documenting changes consistent with chronic hepatitis, all patients were randomized to receive either interferon 3 MIU 3 times/week plus ribavirin 1000-1200 mg/kg vs interferon 5 MIU 3 times/week plus ribavirin same dosage. Patients were treated for 24 weeks at which time an HCV RNA determination was obtained. Patients with a positive HCV RNA at 24 weeks were discontinued from the study, while those with a negative HCV RNA continued therapy for an additional 24 weeks. The rates of sustained viral response (defined as an undetectable HCV-RNA 6 months after completing therapy), in the 2 groups were as follows: 28% for patients who received the standard interferon dose, and 37% for those who received the high-dose interferon. Patients with genotype 1 had a 10% sustained response to standard therapy, whereas the genotype 1 response in the high-dose interferon group was 37%. Genotype 2 and 3 infected patients had an overall sustained response rate greater than 80%.

The paper published by Jaeckel E, et al¹⁷ showing that treatment of acute hepatitis C with IFN alfa-2b for 20 weeks prevents chronic infection in 98% of acutely infected persons seems to suggest that the sooner the treatment is started the better with greater chances of success. Indeed even balancing the disadvantages of IFN therapy postponing treatment for HCV infection waiting for the damage to occur does not seem, to this reviewer, a rational medical decision with dubious ethical implications. Lessons learned from HIV early treatment should be carefully considered.

Treatment of the Cirrhotic Patient (*see note to previous paragraph*).

Helbing and colleagues¹⁸ reported the preliminary results of a multicenter Swiss study evaluating the treatment of patients with bridging fibrosis and cirrhosis with a combination of pegylated interferon alfa-2a plus ribavirin. Patients are being randomized to receive pegylated interferon alfa-2a at a dose of 180 µg/week plus either ribavirin 1000-1200 mg/day or ribavirin 600-800 mg/day (a dosage for which rationale seems lacking). To date, 88 patients have been enrolled in the trial. At 24 weeks on therapy, 87% of patients have had an on-treatment response, defined as an undetectable serum HCV RNA. HCV RNA was undetectable in 93% of those patients in the high-dose ribavirin arm. Ten patients (a significant number compared to other reports) stopped therapy due to adverse events. These interim results are encouraging,

but the final sustained response rates must be used in assessing the relevance of these findings.

Conclusions. It seems that addition of Ribavirin at high doses (those which are considered now as standard therapy) plus IFN can achieve some result in cirrhotic patients a group facing relevant therapeutical problems, with apparent increase of toxic effects. Data on PEG-IFN + ribavirin are still lacking.

Treatment of Relapser and Nonresponder Patients

Several papers were presented during the 2002 Digestive Disease Week meeting discussing the use of pegylated interferons for the treatment of non-responders and relapsers to previous antiviral therapy.

The New York Peg-Intron[®] Study Group¹⁹ discussed preliminary data from a trial comparing 2 different dose regimens of pegylated interferon alfa-2b plus ribavirin in nonresponder and relapse patients. (Relapse patients are those who develop an end-of-treatment response and following cessation of therapy have detectable HCV RNA. Non-responders included patients treated with previous antiviral therapies who did not achieve an undetectable HCV RNA.) Group 1 received pegylated interferon alfa-2b 1.0 µg/kg plus ribavirin 1000-1200 mg/day; Group 2 received pegylated interferon alfa-2b 1.5 µg/kg plus ribavirin 800 mg/day. To date, 131 patients have completed the trial. The total sustained viral response of all patients completing follow-up was 21%. The overall sustained viral response of blacks infected with genotype 1 was a disappointing 8%. The sustained viral response in previous non-responders to combination therapy for patients in group 1 and group 2 was 10% and 11%, respectively. The sustained viral response in previous non-responders to interferon monotherapy for patients in group 1 and group 2 was 40% and 25%, respectively. The sustained viral response in previous relapsers to combination therapy for those in group 1 and group 2 was 43% and 60%, respectively. Patients with more advanced fibrosis achieved better response rates with the higher dose of pegylated interferon. The preliminary data presented in this study are encouraging in relapse patients treated with higher-dose pegylated interferon. Non-responders to previous combination therapy appear to have a poor response to combination pegylated interferon plus ribavirin. The final say on this study will become apparent when the complete trial data are released.

Lawitz and colleagues²⁰ also reported on the use of induction dose of pegylated interferon alfa-2b plus ribavirin in the treatment of previous non-responders to combination standard interferon plus ribavirin therapy. Four hundred seventy-three non-responders to combination therapy, 108 non-responders to interferon monotherapy, and 99 relapsers to combination therapy were enrolled. Subjects were randomized into 2 groups: Group 1 (the induction arm) patients received pegylated interferon alfa-2b 1.5 µg/kg/week plus ribavirin 1000-1200 mg/day for 12 weeks followed by pegylated interferon alfa-2b 1.0 µg/kg/week plus ribavirin 800 mg/day for another 36 weeks; Group 2 or the fixed-dose patients received pegylated interferon alfa-2b 1.0µg/kg/week plus ribavirin for 48 weeks. The end-of-treatment viral response rates for non-responders to combination therapy for the induction and fixed-dose groups were 25% and 16%, respectively. The end-of-treatment viral response rates for non-responders to interferon monotherapy for those in the induction and fixed dose groups were 34% and 30%, respectively. The end-of-treatment viral

response rates for relapsers to combination therapy for patients in the induction and fixed-dose groups were 55% and 58%, respectively.

Randomised trials comparing interferon versus control or different interferon regimens in chronic hepatitis C patients being non responders and relapsers to previous interferon have been evaluated by the Cochrane group²¹ using as primary outcome the failure to achieve a sustained virologic response (defined as positive serum hepatitis C virus RNA at least six months following treatment). No studies using PEG-IFN have been yet critically reviewed in these groups of patients.

Ten randomised trials involving 686 non-responders and eight trials involving 484 relapsers were included; their methodological quality was poor. In non-responders, interferon reduced the risk of not achieving an end of treatment biochemical response compared with no treatment (relative risk [RR] 0.77, 95% confidence interval [CI] 0.66 to 0.91); however, virologic responses were not reported. In a *post hoc* subgroup analysis, doses greater than 3 million units (MU) three times weekly offered no advantage compared with 3 MU three times weekly for biochemical sustained response. Failure to obtain a virologic sustained response was less likely with 48 than 24 weeks of therapy (RR 0.87, 95% CI 0.79 to 0.96).

CONCLUSIONS

It can be concluded that retreatment with interferon leads to sustained virologic clearance in a minority of chronic hepatitis C patients with non-response or relapse following interferon monotherapy. Treatment durations of 48 weeks are superior to 24 weeks, but doses greater than 3 MU three times weekly are no more effective. No published data are still available on retreatment with PEG-IFN plus ribavirin. Data presented at the American Association for the Study of Liver Disease November 2001, Dallas by Afdhal N, *et al* indicate an additional response to PEG-IFN/Ribavirin of 25% in previous non-responders and 61% in relapsers after an initial course of IFN /Rebetron therapy.

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