

HCV QUARTERLY JOURNAL REVIEW

a publication of the Hepatitis C Support Project

September 2003




Issue 1

Alan Franciscus









Editor-in-Chief

In This Issue:

Diagnostics:

-  Comparison of Three Commercially Available Assays for HCV RNA Using the International Unit Standard: Implications for Management of Patients with Chronic Hepatitis C Virus Infection in Clinical Practice
-  Clinical Relevance of Total HCV Core Antigen Testing for Hepatitis C Monitoring and for Predicting Patients' Response to Therapy
-  Biochemical Surrogate Markers of Liver Fibrosis and Activity in a Randomized Trial of Peginterferon Alfa-2b and Ribavirin

Hepatitis C Therapy

-  A Multicenter Study of Recombinant Human Interleukin 12 for the Treatment of Chronic Hepatitis C Virus Infection in Patients Non-Responsive to Previous Therapy
-  High Sustained Virological Response in Chronic Hepatitis C by Combining Induction and Prolonged Maintenance Therapy
-  Effects of Alpha Interferon Induction plus Ribavirin With or Without Amantadine in the Treatment of Interferon Non-Responsive Chronic Hepatitis C: A Randomised Trial
-  Reinforced Interferon Alpha-2b and Ribavirin is More Effective than Standard Combination Therapy in the Retreatment of Chronic Hepatitis C Previously Nonresponsive to Interferon: A Randomized Trial
-  Twelve Weeks of Follow-up is Sufficient for the Determination of Sustained Virologic Response in Patients Treated with Interferon-a for Chronic Hepatitis C
-  Regression of Fibrosis in Chronic Hepatitis C after Therapy with Interferon and Ribavirin
-  Dynamics of Alanine Aminotransferase During Hepatitis C Virus Treatment
-  Effect of Treatment with Peginterferon or Interferon Alfa-2b and Ribavirin on Steatosis in Patients Infected with Hepatitis C

Hepatitis C: Natural History and Pathogenesis

-  Predicting Progression to Cirrhosis in Chronic Hepatitis C Virus Infection
-  Cost-Effectiveness of Treatment for Chronic Hepatitis C Infection in an Evolving Patient Population

Comparison of Three Commercially Available Assays for HCV RNA Using the International Unit Standard: Implications for Management of Patients with Chronic Hepatitis C Virus Infection in Clinical Practice

Mitchell L. Shiffman, M.D., Andrea Ferreira-Gonzalez, Ph.D., K. Rajender Reddy, M.D., Richard K. Sterling, M.D., Velimir A. Luketic, M.D., R. Todd Stravitz, M.D., Arun J. Sanyal, M.D., Carleton T. Garrett, M.D., Ph.D., Maria De Medina, M.S.P.H., and Eugene R. Schiff, M.D.—Hepatology Section, USA and Division of Molecular Diagnostics, Virginia Commonwealth University Health System—Medical College of Virginia, Richmond, Virginia; Division of Gastroenterology and Hepatology, University of Pennsylvania, Philadelphia, Pennsylvania; and Center for Liver Diseases, University of Miami, Miami, Florida

Source: *The American Journal of Gastroenterology* Vol. 98, No 5, 2003

Introduction

HCV RNA (viral load) testing is used to confirm active infection in patients who test positive for HCV antibodies (anti-HCV) and during treatment to confirm that the viral load is decreasing or is undetectable during and after HCV therapy. Viral load testing during treatment can identify patients who are unlikely to achieve an sustained virological response allowing the physician and the patient to decide if treatment should be discontinued.

Objective

The aim of this study was to evaluate the impact of the international unit standard for measuring HCV RNA (viral load) in the management of patients with chronic hepatitis C (HCV) infection.

Patients

This small prospective study of 106 patients (mean age -44 yo), male (62%), African American (24%), bridging fibrosis or cirrhosis (38%), genotype 1 (75%) received interferon and ribavirin for 6 to 12 months, depending on genotype.

Methods

Three assays were used—Amplicor Monitor PCR, the National Genetics Institute PCR assay, and branched chain DNA. Viral load was measured at four points (baseline, 3 months after the start of therapy, at the end of treatment, and 6 months after discontinuation of therapy). Four hundred and twenty four samples were analyzed.

Results

Of the sample analyzed, 82-89% of values were within 1 log unit and 85-92% were within 2 log units by the various assays. This variability was not dependent upon HCV genotype. HCV RNA (viral load) was undetectable in 1.4-6.8% of samples when virus was detected by another assay. The mean viral load in these discordant samples was 1.47-6.33 log IU/ml (30-2,100,000 IU/ml).

Conclusion

The authors concluded that their data demonstrated approximately 90% of serum values for HCV RNA (viral load) were within 1 log unit by the international unit standard regardless of which viral load test was used. However, false positive and false negative results as well as variations in viral load level of more than 1 to 2 logs units can occur with any of the assays, and these results may have an impact upon the management of patients receiving HCV medications. It is therefore unwise to base important treatment decisions based on a single viral load determination.

Clinical Relevance of Total HCV Core Antigen Testing for Hepatitis C Monitoring and for Predicting Patients' Response to Therapy

M. Maynard, P. Pradat, P. Berthillon, G. Picchio, N. Voirin, M. Martinot, P. Marcellin and C. Trepo - Hdtel-Dieu, Lyon, France; Clinical Diagnostics, Raritan, NJ, USA; U271, Lyon, France; and U 483, Hopital Beau Jon, Paris, France

Source: *Journal of Viral Hepatitis*, 2003, 10, 318-32

Introduction

Diagnosing HCV infection is accomplished by a combination of the detection of the HCV antibody test and the HCV-RNA (viral load) test. Monitoring treatment is usually assessed by measuring HCV-RNA (viral load) and to a lesser extent alanine aminotransferase levels (ALT, biochemical response). The recently developed ELISA method for detection of HCV Core protein has been shown to be useful in the quantitative evaluation of HCV viral load. This method appears to show sensitivity and specificity comparable to that of commercially available viral load test, correlates well with these assays regardless of genotype, appears to be suitable for large-scale screening of blood donations, and for monitoring the response of interferon treatment.

Objective

To study the correlation between total Hepatitis C virus (HCV) Core antigen (Ag) and HCV-RNA, and to assess the proficiency of HCV Core Ag testing in monitoring and predicting virologic response during and after pegylated interferon (PEG-IFN) and ribavirin combination therapy.

Patients/ Methods

This is a single-center, prospective study. A total of 307 samples from treated and untreated patients were used to assess the correlation between the total HCV Core Ag test and quantitative HCV-RNA assays (Superquant, and Quatiplex branched DNA 2.0 assay).

Twenty-four patients received combination therapy for 48 weeks. Blood samples were collected at day 0, and week 2, 4, 12, 24, 48 and 72 for virologic evaluation.

Results

A linear relation exists between total HCV Core Ag and HCV-RNA levels. At 3 months the positive predictive value (PPV) of response to therapy was 100% with either HCV

Core Ag or HCV-RNA. For HCV Core Ag the negative predictive value (NPV) was 100% whereas for HCV-RNA the NPV was 80% ($P > 0.05$).

At month 1, the PPV was 95% and 100% when determined by HCV Core Ag and HCV RNA, respectively. The NPV value was 100% for HCV Core Ag and 33% for HCV-RNA ($P = 0.005$).

HCV Core Ag quantification could be useful in clinical practice to predict a sustained virological response early during therapy (4 weeks), reaching an optimal performance at month 3.

Conclusion

The determination of total HCV Core Ag levels in serum constitutes an accurate and reliable alternative to HCV-RNA for monitoring and predicting treatment outcome in patients receiving PEG-IFN/ribavirin combination therapy.

Biochemical Surrogate Markers of Liver Fibrosis and Activity in a Randomized Trial of Peginterferon Alfa-2b and Ribavirin

Thierry Poynard, John McHutchison, Michael Manns, Rob P. Myers, and Janice Albrecht

Hepatology, Vol. 38, No. 2, 2003

Introduction

In patients infected with hepatitis C virus (HCV), some recent studies have shown the predictive value of combinations of simple serum biochemical markers: *Fibrotest (FT)* for the diagnosis of significant fibrosis (ranging from few septa to cirrhosis) and *Actitest (AT)* for the assessment of necroinflammatory activity fibrosis and activity.

The liver biopsy is the standard of care in evaluating the health of the liver. The liver biopsy is also important because it can aid the physician and patient in making appropriate HCV management and treatment decisions. In addition repeated biopsies can be used to determine disease progression over a period of time.

Objective

The primary aim of this multicenter, respective study was to assess the diagnostic value of FT-AT in patients at baseline and at end of follow-up. In contrast to previous reports, the METAVIR and Knodell scoring systems, including the components of the histologic index. The secondary aims were to assess the variation of FT-AT according to virologic response; to assess the concordance between FT-AT and histologic variations; to compare a decision algorithm without liver biopsy; and lastly to compare FT-AT and liver biopsy as trial end points for evaluating histologic impact.

Patients/ Methods

A total of 1,530 patients from a randomized trial comparing three interferon plus ribavirin combination treatments were considered for this retrospective study. Patients were

previously untreated for their hepatitis C, had HCV RNA detectable in the serum, and had elevated alanine aminotransferase (ALT) levels.

Treatment consisted of either interferon 3 MU three times a week and ribavirin (1,000 mg if weight below 75kg, 1,200 mg greater than 75 kg) or the new combination of 1.5 µg/kg peginterferon and ribavirin (800 mg) for 48 weeks.

Three hundred fifty-two patients who had had 2 interpretable liver biopsies (at baseline and at 24 week follow-up) and stored blood samples before and after treatment were selected.

One hundred forty-four patients received the standard interferon and ribavirin therapy and 208 received the peginterferon plus ribavirin treatment.

FT markers include α_2 -macroglobulin, haptoglobin, γ -glutamyl transpeptidase (GGT), total bilirubin and apolipoprotein A1. The AT combines the 5 markers for FT plus ALT.

Results

The analysis of the data showed that FT-AT gave similar results to liver histology. The biochemical markers were found to be highly predictive of the health of the liver with a higher power for the biochemical markers.

The biochemical markers have significant predictive values both for the diagnosis of fibrosis and for activity. FT-AT increases parallel the increase in fibrosis stage and activity grade. Comparing the different treatment regimes found that patients who achieved an SVR for both therapies showed 3 significant differences between FT values before and after treatment.

Conclusion

The authors concluded that biochemical markers have improved and should now be considered both for the initial evaluation and for follow-up. The authors believe that a biopsy should not be mandatory due to the limits and risk of biopsy. It was also recommended conducting a prospective randomized trial of 2 strategies comparing a strategy without and with biopsy to confirm the results of this trial. However, they noted that it would require a large number of patients to estimate the severe adverse events. Finally, the authors concluded that a simplification of liver damage assessment should accelerate the management of chronic hepatitis C.

A Multicenter Study of Recombinant Human Interleukin 12 for the Treatment of Chronic Hepatitis C Virus Infection in Patients Non-Responsive to Previous Therapy

Paul J. Pockros, Keyvr Patel!, Christopher O'Brien, Myron Tong, Coleman Smith, Vinod Rustgi, Robert L. Carrithers, John G. McHutchison, Elizabeth Olek, and Michael F. DeBruin

Source: *Hepatology*, Vol.37, No. 6, 2003

Introduction

Recombinant human interleukin 12 (IL-12) is an immunomodulatory cytokine that is active against several viruses. Treatment options are limited in patients with chronic hepatitis C with nonresponse to previous interferon (IFN)-based therapy. Prior dose-ranging studies have indicated drug tolerability and transient suppression of hepatitis C virus (HCV) RNA by IL-12.

Objective

The aim of this study was to determine the safety and efficacy of prolonged IL-12 therapy in patients who have failed treatment with IFN-a with or without ribavirin.

Patients/ Methods

A total of 225 patients at 21 U.S. sites who had a history of nonresponse to IFN-a or combination IFN-a plus ribavirin for treatment of HCV were randomized to 500 ng/kg IL-12 or placebo subcutaneously twice weekly for 12 weeks.

The groups were then unblinded. The patients receiving IL-12 continued for another 36 weeks, and the placebo group received 48 weeks of treatment with IL-12 in an open-label fashion.

HCV RNA, serum alanine aminotransferase (ALT) level, and a repeat liver biopsy were assessed at 24 weeks following therapy.

Results

Approximately 1% (2 of 160) of nonresponsive patients enrolled for treatment had a sustained virologic response to IL-12 therapy, but 3% (7 of 225) developed severe adverse events probably related to treatment, resulting in early termination of the trial.

Common adverse effects reported by most patients included chills, fever, fatigue, headache, and arthralgia (joint pain).

At termination of the study, 160 patients had received at least 8 weeks of treatment with IL-12. Paired liver biopsy specimens were available for evaluation in 54 patients, but there were no significant changes in Knodell fibrosis or histologic activity index (HAI) scores.

Conclusion

The authors concluded that IL-12 as monotherapy at the doses used in this trial for chronic hepatitis C reported low efficacy, was poorly tolerated, and is unlikely to provide an alternative to conventional interferon based therapy.

High Sustained Virological Response in Chronic Hepatitis C by Combining Induction and Prolonged Maintenance Therapy

J.M. Vrolijk, F.C. Bekkering, J.T. Brouwer, Hansen B, and Schalm S.

Source: *Journal of Viral Hepatitis*, 10, 205-209 (2003)

Introduction

The most difficult to treat HCV patients are those with genotype 1 infection, high viral load, cirrhosis or those that have not previously responded to prior treatment of HCV with interferon and ribavirin.

Objectives

The authors studied the treatment regime that combines high dose induction interferon (IFN) followed by prolonged daily interferon and ribavirin treatment in these difficult to treat patients.

Patients

This was a small prospective study of 24 patients (male=17), mean age 47 YO, with genotype 1 (11 pts), cirrhosis (11 pts), previous non-responders to interferon (15), high viral load (17) or a combination of these characteristics in a single center study. These patients were estimated to have less than a 30% chance of achieving a sustained virological response rate.

Methods

Patients were treated with 10 million units (MU) daily for four weeks followed by 5 MU/day until week 4, 3 MU/day until week 52 and 3 MU three times a week until week 76 in combination with 1-1.2 grams ribavirin daily.

Note: This is the first study in which patients were treated with daily high-dose induction for longer than 12 weeks.

HCV viral load levels were taken weekly until week 4 and at least once every 3 months for the remainder of the treatment period using a viral load test with a detection limit below 500 copies/mL.

Results

Intention to Treat Analysis (SVR):

	Number of Patients	SVR
All	24	16 (67%)
Genotype		
Non-1	13	10 (77%)
1	11	6 (55%)
Cirrhosis		
Absent	13	12 (92%)
Present	11	4 (36%)

Response to previous treatment		
Nonresponder	14	10 (71%)
Relapser /naive	10	6 (60%)

Per Protocol Analysis (SVR):

	Number of Patients	SVR
All	20	16 (80%)
Genotype		
Non-1	11	10 (91%)
1	9	6 (67%)
Cirrhosis		
Absent	12	12 (100%)
Present	8	4 (50%)
Response to previous treatment		
Nonresponder	13	10 (77%)
Relapser/naive	7	6 (60%)

Note: SVR was achieved in almost all of patients without cirrhosis

Summary/ Conclusion

The authors found that the virological response occurred rapidly (< 8 weeks of treatment) in all patients with a sustained virological response rate. The relapse rate after stopping therapy was only 5%. Side effects were seen frequently—six patients had to be hospitalized (5 out of 6 had cirrhosis).

The authors concluded that this new treatment of induction and prolonged daily interferon plus ribavirin therapy produced a high SVR in patients who are less likely to respond to HCV medications (genotype 1, cirrhosis, high viral load or previous non-response to therapy or combination of these characteristics). In addition the authors recommended that further research is needed to evaluate this regime in larger controlled studies that include pegylated interferon and ribavirin in this patient population.

Effects of Alpha Interferon Induction plus Ribavirin With or Without Amantadine in the Treatment of Interferon Non-Responsive Chronic Hepatitis C: A Randomised Trial

I E Adinolfi, R Utili, A Tonziello, G Ruggiero

Source: *Gut* 2003;52:701—705

Introduction

Fifty per cent of chronic hepatitis C patients are non-responders to interferon based therapy. At present, there are no recommended therapeutic options for non-responders.

Objectives

The aim of this single center, prospective, open label study was to evaluate the safety and long term effect of alpha interferon induction therapy plus ribavirin with or without amantadine in the treatment of interferon non-responsive chronic hepatitis C.

Patients/Methods

A total of 114 consecutive patients were randomly divided into three groups with a final 2:2:1 ratio:

- * Group A (44 patients – Genotype 1 – 70%) received interferon alfa 2b, 3 million units (MU), three times a week, and oral ribavirin (1000 mg/day);
- * Group B (46 patients – Genotype 1 – 72%) received interferon 3 MU daily for the first four weeks and subsequently 3 MU three times a week, and ribavirin as in regimen A;
- * Group C (24 patients – Genotype 1 – 71%) received interferon and ribavirin as in regimen B, plus oral amantadine hydrochloride (200 mg/day). The duration of treatment was 12 months.

Results

The end of treatment response for groups A and B was 25% and 29%, respectively, and for group C, 68% ($p < 0.05$) at the end of one year of follow up, a sustained response was observed for six (25% SVR - genotype 1 – 13%) patients in group C, one (2% SVR - genotype 1 – 3%) patient in group A, and two (4% SVR - genotype 1 – 0%) patients in group B ($p < 0.002$).

The triple regimen was well tolerated and did not increase the frequency or severity of side effects.

Conclusion

The authors concluded that their study demonstrates that for the treatment of interferon non-responder hepatitis C patients, the association of interferon plus ribavirin has a negligible long term effect whereas a triple regimen including interferon, ribavirin, and amantadine can be an effective and safe treatment.

Reinforced Interferon Alpha-2b and Ribavirin is More Effective than Standard Combination Therapy in the Retreatment of Chronic Hepatitis C Previously Nonresponsive to Interferon: A Randomized Trial

T. Poynard, P. Marcellin, A. Bissery, R. P. Myers, J. Moussallj, F. Degos, D. Dhumeaux, G. Riachi, J. P. Bronowicki, P. Brissot, c. Buffet, L. Serfaty, S. Naveau, P. Sogni, M. Beaugrand, S. Gayno, D. Larrey, D. Samuel, C. Eugene, S. Pol, P. Bedossa, V. Daurat and P. Chaumet-Riffaud for the multicenter GER-CYT-RIBANON group

Hepatogastroenterology, Groupe Hospitalier Pitié-Salpêtrière, Université Paris 6, CNRS ESA 8067 Paris, France; Beaujon, Clichy; Groupe Hospitalier Pitié-Salpêtrière; Henri Mondor, Créteil; Hopital Charles Nicolle, Rouen; Brabois, Nancy; 7 Pontchaillou, Rennes; Bicêtre, Kremlin Bicêtre; 9 St Antoine, Paris; Hopital Antoine Bécléré, Clamart; Cochin, Paris; Jean Verdier, Bondy; René Dubos, Pontoise; St Eloi Montpellier; Paul Brousse Villejuif; Leon Touh

Introduction

Interferon-alpha (IFN) monotherapy results in sustained virological clearance in a minority of patients (15% SVR) with chronic hepatitis C. Recent studies suggest that higher doses of interferon in combination with ribavirin may increase the rate of response. However, the role of this therapy has yet to be definitively established.

Objectives

The aim of this study was to assess the effect of a *reinforced regimen* combining ribavirin and high-dose interferon for 48 weeks compared with a *nonreinforced regimen* combining a standard interferon regimen and ribavirin for 24 weeks in nonresponders with chronic hepatitis C.

Patients/Methods

A total of 231 patients with chronic hepatitis C and previous non-response to interferon monotherapy were randomized. The *reinforced* group (n = 14) received IFN-2b, 6 million units (MU) thrice weekly (TIW) and ribavirin for 48 weeks, and the *nonreinforced* group (n = 117) received IFN-2b, 3 MU TIW and ribavirin for 24 weeks.

The main outcome measure was a sustained virological response, defined as negative serum hepatitis C virus (HCV)-RNA 24 weeks following the end of treatment. This endpoint was determined in 98 patients of the *reinforced* group and 105 patients of the *nonreinforced* group.

Results

At the end of follow-up, a sustained virological response was observed in 29 of the 98 patients (29.6%) in the *reinforced* group vs 6 of the 105 patients (15.2%) in the *nonreinforced* group (P = 0.014). In multivariate analysis, factors associated with a sustained virological response were treated with a *reinforced* regimen [odds ratio (OR) 2.9; P = 0.06] and genotype 2 or 3 (OR 8.8; P < 0.0002).

A total of 160 patients had paired biopsies before and after treatment. Histological activity improvement was observed in 32 of 80 patients (40%) and fibrosis worsening in 26 of 80 patients (33%) in the *reinforced* group vs 13 of 80 (16 %) and 19 of 80 (24%) in the *nonreinforced* group (P = 0.30 and 0.20, respectively).

Although significantly more effective, tolerance of the high-dose, prolonged duration regimen was poor. In comparison to standard treatment, more patients receiving the *reinforced* regimen were hospitalized for serious adverse events and nearly three times as many discontinued treatment prematurely (30% vs. 11%). The authors noted that this increase in adverse events was not observed in a recent trial comparing peginterferon plus ribavirin vs. standard interferon plus ribavirin therapy and could be explained by the action of pegylated interferon in minimization of fluctuations of interferon levels.

Conclusion

The authors concluded that in nonresponders, a high-dose 48-week regimen of IFN and ribavirin combination was more effective than a regimen with interferon at lower dose and ribavirin for 24 weeks only.

Twelve Weeks of Follow-up is Sufficient for the Determination of Sustained Virologic Response in Patients Treated with Interferon-a for Chronic Hepatitis C

Stefan Zeuzeml, E. Jenny Heathcote, Mitchell L. Shiffman, Teresa L. Wright, Vincent G. Bain, Morris Sherman, S. Victor Feinman, Michael W. Fried, Jens Rasenack, Christoph Sarrazin, Donald M. Jensen, Amy Lin, Joseph H. Hoffman, Farhad Sedarati

Homburg/Saar, Germany, Toronto, Toronto, ON Canada, College of Virginia Commonwealth University, Richmond, VA, USA, California San Francisco, San Francisco, CA, USA, University of Alberta, Edmonton, AR Canada, General Hospital, Toronto, ON Canada, Sinai Hospital, Toronto, ON Canada, University of North Carolina, Chapel Hill, NC, USA, Clinic of Freiburg, Freiburg, Germany, Rtesh-Presb Luke's Medical Center, Chicago, IL, USA, Hoffmann-La Roche, Nutley, NJ, USA

Journal of Hepatology 39 (2003) 106-111

Introduction

The current standard for the determination of sustained virologic response in patients treated for hepatitis C is undetectable hepatitis C virus (HCV) RNA 24 weeks following the completion of therapy. Sensitive molecular tests may permit earlier determination of sustained virologic response following the completion of therapy in end-of-treatment responders.

Methods

This was a retrospective study of previous phase II/III clinical trials in which 132 of 566 (23%) received standard interferon for 48 weeks and had end of treatment response, while 492 of 875 (56%) patients received pegylated interferon a-2a for 48 weeks and had end of treatment response. At the end of follow-up, 80 interferon alpha 2a patients achieved a sustained virological response (SVR) compared to 262 pegylated interferon a-2a. HCV RNA (viral load) was determined by polymerase chain reaction assay (Amplicor HCV Monitor vs. 2.0) at baseline and monitored at 4-week intervals throughout the treatment and 24-week post-treatment follow-up periods.

Results

End-of-treatment and sustained response (24 week follow-up) were achieved in 624 and 342 patients, respectively. For all treatments, relapse was most frequent at weeks 52 and 56 and became rare following week 60. Only six patients out of 348 patients (2%) became HCV RNA positive between weeks 60 and 72. An analysis of baseline characteristics was conducted but failed to identify any specific factors associated with early or late response.

Conclusion

The authors concluded that this finding suggests that determination of HCV RNA levels at 12 weeks of follow-up may be sufficient for making decisions related to the management of most patients treated with standard or pegylated interferon *a*.

Regression of Fibrosis in Chronic Hepatitis C after Therapy with Interferon and Ribavirin

Asma Arif, MD, Robert A. Levine, MD, Schuyler O. Sanderson, MD, Leslie Bank, MD, Raja P. Velu PHD, Ashok Shah, MD, Thomas C. Mahl, MD and Daniel H. Gregory, MD.

Digestive Diseases and Sciences, Vol. 48, No. 7 (July 2003), pp. 1425-1430 (© 2003)

Introduction

Interferon and ribavirin decrease necroinflammation in chronic hepatitis C with or without virological clearance; however, reversibility of fibrosis remains to be established.

Objective

In this retrospective study, the authors evaluated the effect of combination therapy (interferon and ribavirin) on virological and liver histopathological outcomes in 52 treatment naïve patients and 79 patients unresponsive to interferon monotherapy.

Methods

One hundred four patients (predominately genotype 1) completed interferon and ribavirin treatment after 24-48 weeks. Fifty-six paired liver biopsies (mean biopsy interval 28 months) were assessed by the Ishak score. Sustained virological response (SVR) rates were 37% in naïve patients and 22% in re-treated patients.

Results

In virological responders and nonresponders, fibrosis and necroinflammation scores decreased by -0.91 (P = 0.04) and -0.5 (P = 0.02) and by -2.8 (P = 0.001) and -0.66 (P = 0.06), respectively.

Conclusion

The authors concluded that combination therapy improves fibrosis in both virological responders and nonresponders and treatment strategies in virological non-responders who show fibrosis regression should include consideration of maintenance therapy, if such treatment eventually proves to benefit histological outcomes. In addition they commented that efficacy should not only judged by “virological cure” 24 weeks after combination therapy, but by fibrosis regression.

Dynamics of Alanine Aminotransferase During Hepatitis C Virus Treatment

Ruy M. Ribeiro, Jennifer Layden-Alrner, Kimberly A. Powers, Thomas J. Layden, and Alaii S. Perelson

Hepatology 2003;38:509-517

Introduction

Studies of the kinetics of hepatitis C virus (HCV) decline during interferon (IFN)-based therapy have led to insights into treatment efficacy. However, the kinetics of serum alanine aminotransferase (ALT), an enzyme used as a surrogate of liver damage, have not been closely monitored, and it is not known if they correlate with those of HCV RNA.

Objective

The objective of this prospective study was to identify the association between ALT and HCV RNA (viral load) dynamics.

Methods

The authors analyzed 35 patients treated daily with 10 MIU IFN- α 2b with or without ribavirin for 28 days followed by standard interferon plus ribavirin therapy.

Results

Patients exhibited 4 patterns of ALT change:

- (1) exponential decay of ALT,
- (2) transient increase in ALT followed by a decrease to pretreatment or normal levels,
- (3) increase in ALT to a new level, and
- (4) no significant change.

By simultaneously modeling HCV and ALT dynamics, we successfully fit the observed changes. The authors found ALT decays with $t_{1/2}=12.7$ hours. The transient increase in ALT observed in some patients suggested a mild hepatotoxic effect of interferon. However, patients with a smaller initial ALT increase achieved higher rates of viral negativity by week 72 ($P = .02$). The week-4 ALT decline correlated with the HCV log drop ($P=.006$) and the efficacy of therapy ($P=.025$).

Conclusion

The authors found that the results suggest the use of ALT as a surrogate marker for treatment effect in patients with elevated ALT is consistent with prior studies with standard interferon.

Effect of Treatment with Peginterferon or Interferon Alfa-2b and Ribavirin on Steatosis in Patients Infected with Hepatitis C

Thierry Poynard, Viad Ratziu, John Mdlutchison, Michael Manns, Zachary Goodman, Stefan Zeuzem, Zobair Younossi, and Janice Albrecht

Hepatology 2003; 38: 75-85

Introduction

It has been suggested that hepatitis C virus (HCV) and especially genotype 3 is associated with steatosis. One strong argument for a direct effect of the hepatitis C virus is the disappearance of steatosis with the disappearance of the virus in patients who were treated with interferon or interferon and ribavirin.

Aim

The aim of this study was to assess the impact of sustained virologic response on steatosis using a large database of patients with paired biopsies recently included in a multicenter randomized trial of pegylated interferon (peginterferon alfa-2b) and ribavirin combination. This specific aims were:

- (1) to assess the prevalence of steatosis
- (2) to assess factors associated with steatosis including infection with genotype 2
- (3) to assess the impact of steatosis on treatment response, and
- (4) to assess the impact of treatment on steatosis

Patients/Methods

The authors analyzed 1,428 naïve patients included in a randomized trial. A single pathologist scored steatosis at baseline and 24 weeks after the treatment.

Results

At baseline, steatosis was present in 935 of 1,428 patients (65%), including 175 (83%) of 210 patients with genotype 3 versus 760 (62%) of 1,218 with other genotypes ($P < .001$). The variables associated with steatosis in logistic regression were genotype 3 ($P < .001$), triglycerides greater than 1.7 mmol/L ($P < .001$), body mass index greater than 27 ($P < .04$), age greater than 40 years ($P < .001$), and septal fibrosis ($P = .007$).

In genotype 3-infected patients, steatosis was associated with high viral load and with lower serum cholesterol. Steatosis was associated with lower sustained response rate, even after taking into account other factors ($P < .001$). Among virologic responders, steatosis was much improved in genotype 3, improvement of at least 1 grade in 77%, and disappearance in 46% compared with other genotypes, 46% and 29%, respectively ($P < .001$ both comparisons). In genotype 3 responders, the baseline low serum cholesterol was corrected by treatment ($P < .001$). Steatosis was associated with HCV genotype 3, triglycerides, high body mass index, age, fibrosis stage, and lower virologic response to treatment.

Conclusion

The authors concluded that sustained disappearance of the hepatitis C virus is associated with reduction of steatosis in genotype 3 as well as a correction of baseline low serum cholesterol.

Predicting Progression to Cirrhosis in Chronic Hepatitis C Virus Infection

A. J. Freeman, M. G. Law, J. M. Kaldor and C. J. Dore National Centre in HIV Epidemiology and Clinical Research, The University of New South Wales, Sydney, Australia

Journal of Viral Hepatitis, 2003, 10, 285-293

Introduction

Predicting progression to cirrhosis is highly variable. Identifying factors that influence outcome is important in order to counsel patients regarding their prognosis and to help with disease management.

Objective

To identify what factors influence HCV liver disease progression and evaluate the consistency of cofactors across study settings.

Note: This study did not examine co-infection with HIV or HBV but the authors commented that these coinfections would most likely result in worse outcomes for patients with chronic HCV infection.

Methods

The authors assessed a systematic evaluation of published studies to identify factors associated with accelerated fibrosis progression in patients with chronic hepatitis C virus (HCV) infection. An ecologic analysis was used to estimate relative risk (RR) of cirrhosis across four study methodologies:

- (1) liver clinic series,
- (2) post-transfusion cohorts,
- (3) community- based studies and
- (4) blood donor series. In each study category.

Results

The following factors were independently associated with disease progression:

- (1) male sex (RR = 1.08);
- (2) heavy alcohol consumption (RR = 1.61);
- (3) elevated serum ALT levels (RR = 1.23) and
- (4) histology demonstrating high-grade necro inflammatory activity.

Virological factors such as HCV genotype, viral load and quasispecies diversity were also examined. A Weibull distribution was used to model disease progression at a population level. The influence of cofactors on individual prognosis was examined and an algorithm to predict the risk of subsequently developing cirrhosis is presented.

The authors found that four factors were identified as influencing progression in chronic HCV infection:

- (1) Gender – Male
- (2) Heavy alcohol consumption (>50g alcohol/day)
- (3) Elevated ALT
- (4) HAI score
- (5) Age at infection

After adjusting for these cofactors, older age at HCV infection and acquisition of HCV through blood transfusion were not implicated in influencing disease outcome.

Conclusion

The authors concluded that despite the limitations of ecologic analyses, the relative risk of fibrosis progression can be attributed to specific cofactors in their study and can be used to estimate risk of cirrhosis from the time of infection. However, it was noted that since the vast majority of people with chronic HCV infection present with established liver disease in these studies, further models are needed to predict both current stage of disease and predict future risk of disease progression.

Cost-Effectiveness of Treatment for Chronic Hepatitis C Infection in an Evolving Patient Population

Joshua A. Salomon, PhD, Milton C. Weinstein, PhD, James K. Hammitt, PhD, Sue J. Goldie, MD, MPH

JAMA, July 9, 2003—Vol 290, No. 2

Introduction

Approximately 2.7 million US individuals are chronically infected with the hepatitis C virus (HCV). As public health campaigns are pursued, a growing number of treatment candidates are likely to have minimal evidence of liver damage.

Objective

The objective of this study was to examine the clinical benefits and cost-effectiveness of newer treatments for chronic hepatitis C infection in a population of asymptomatic, HCV seropositive, but otherwise healthy individuals.

Design and Setting

Cost-effectiveness analysis using a Markov model of the natural history of HCV infection and impact of treatment. We used an epidemiologic model to derive a range of natural history parameters that were empirically calibrated to provide a good fit to observed data on both prevalence of HCV seropositivity and time trends in outcomes related to HCV infection.

Patients/Methods

Patients Cohorts of 40-year-old men and women with elevated levels of alanine aminotransferase (ALT), positive results on quantitative HCV RNA assays and serologic tests for antibody to HCV, and no histological evidence of fibrosis on liver biopsy.

Interventions

Monotherapy with standard or pegylated interferon alfa-2b; combination therapy with standard or pegylated interferon plus ribavirin.

Main Outcome Measures

Lifetime costs, life expectancy, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios.

Results

The probability of patients with chronic HCV developing cirrhosis over a 30-year period ranged from 13% to 46% for men and from 1% to 29% for women. The incremental cost-effectiveness of combination therapy with pegylated interferon

- (1) Men ranged from \$26,000 to \$64,000 per QALY for genotype 1 and from \$10,000 to \$28,000 per QALY for other genotypes;
- (2) Women ranged from \$32,000 to \$90,000 for genotype 1 and from \$12,000 to \$42,000 for other genotypes.

Because the benefits of treatment were realized largely in the form of improvements in health-related quality of life, rather than prolonged survivorship, cost-effectiveness ratios expressed as dollars per year of life were substantially higher. Results were most sensitive to assumptions about the gains and decrements in health-related quality of life associated with treatment.

Conclusion

The authors concluded that while newer treatment options for hepatitis C appear to be reasonably cost-effective on average, these results vary widely across different patient subgroups and depend critically on quality-of-life assumptions. They also noted that as the pool of persons eligible for treatment for HCV infection expands to the more general asymptomatic population, it will be imperative for patients and their physicians to consider these assumptions in making individual-level treatment decisions.