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Sampling Variability of Liver Fibrosis in Chronic Hepatitis C

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Hepatology 2003; 38:1449-1457



Introduction

Fibrosis is a common endpoint of clinical trials in chronic hepatitis C, and liver biopsy remains the gold standard for fibrosis evaluation. However, variability in the distribution of fibrosis within the liver is a potential limitation.

Aim

The aim of this study was to assess the heterogeneity of liver fibrosis and its influence on the accuracy of assessment of fibrosis with liver biopsy.

Methods

Surgical samples of livers from patients with chronic hepatitis C were studied. Measurement of fibrosis was performed on the whole section by using both image analysis and METAVIR score (reference value). From the digitized image of the whole section, virtual biopsy specimens of increasing length were produced. Fibrosis was assessed independently on each individual virtual biopsy specimen. Results were compared with the reference value according to the length of the biopsy specimen.

Results

By using image analysis, the coefficient of variation of fibrosis measurement with 15-mm long biopsy specimens was 55%; and for biopsy specimens of 25-mm length it was 45%. By using the METAVIR scoring system, 65% of biopsies 15 mm in length were categorized correctly according to the reference value. This increased to 75% for a 25-mm liver biopsy specimen without any substantial benefit for longer biopsy specimens.

Sampling variability of fibrosis is a significant limitation in the assessment of fibrosis with liver biopsy.

Conclusion

The authors concluded that this study suggests that a length of at least 25 mm is necessary to evaluate fibrosis accurately with a semiquantitative score. Sampling variability becomes a major limitation when using more accurate methods such as automated image analysis.

Evaluation of a Prison Outreach Clinic for the Diagnosis and Prevention of Hepatitis C: Implications for the National Strategy

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Source: Gut 2003;52: 1500-1504

Introduction

Hepatitis C virus (HCV) infection is a major public health problem recognised by the UK National Strategy that proposes that a care pathway for assessment, diagnosis, and treatment be established in all prisons, integrated within managed clinical networks. A prison sentence provides the opportunity to focus on traditionally hard to reach patients.



Aims

To evaluate the prevalence of HCV infection in a UK prison cluster and to assess the effectiveness of a prison outreach service for hepatitis C.

Patients

1618 male prisoners entered 3 prisons in this 1 year study period.

Patient Characteristics

	Overall % (3 prisons)
Age < 30 years	37.2
Drug offences	19.6
White	69.7
Black	24.1
Asian	2.9
Other	3.3

Methods

A nurse specialist led clinic within a cluster of adult prisons was established, offering health education on hepatitis C, advice on harm minimisation, and HCV testing.

Infected prisoners were offered access to a care pathway leading to treatment. Outcome measures were uptake of the service, and diagnosis and treatment of hepatitis C.

Results

A total of 8.5% of 1618 prisoners accepted testing: 30% had active infection with HCV. Fifty six (97%) admitted to having injected drugs: 19 (33%) while in prison. Forty one (71%) were tattooed. Five (9%) reported having received a blood transfusion prior to 1991. In one subject intranasal drug use was the only identifiable potential exposure to HCV and none of the inmates identified sex with an HCV positive partner as their only exposure to the virus.

Most were ineligible for treatment due to psychiatric illness, persisting high risk behaviours, and failure to biopsy during their prison term. Only 7% of HCV polymerase chain amplification positive inmates received treatment in prison.

Conclusion

There is a large pool of HCV infected prisoners at risk of complications, constituting a source of infection during their sentence and after discharge. A prison outreach clinic and care pathway was perceived as effective in delivering health education, and reducing the burden on prison and hospital services. It provided an opportunity for intervention but had a limited effect in eradicating HCV in prisoners, and it remains unclear how this might be achieved.



Impaired IRS-1/PI3-Kinase Signaling in Patients with HCV: A Mechanism for Increased Prevalence of Type 2 Diabetes

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Source: *Hepatology* 2003;38:1384-1392

Introduction

Patients with hepatitis C virus (HCV) infection have a greater risk of developing type 2 diabetes mellitus. However, the mechanism of this association is unclear.

Aim

In this study, we examined the potential defects in upstream insulin signaling pathways in liver specimens obtained from nonobese/nondiabetic subjects with HCV infection.

Methods

Fasting liver biopsy specimens were obtained from 42 HCV-infected subjects and 10 non-HCV-infected subjects matched for age and body mass index. Liver tissues were exposed to insulin and examined for the contents and phosphorylation/activation status of the upstream insulin signaling molecules by immunoprecipitation and Western blot analysis.

Results

HCV infection resulted in a trend toward a 2-fold to 3-fold increase in insulin receptor (IR) and insulin receptor substrate (IRS)-1 contents when compared with non-HCV. In contrast, insulin-stimulated IRS-1 tyrosine phosphorylation was decreased by 2-fold in HCV-infected subjects compared with non-HCV-infected subjects ($P < .05$).

The observed reductions in IRS-1 tyrosine phosphorylation were accompanied by a 3.4-fold decrease in IRS-1/p85 phosphatidylinositol 3-kinase (PI3-kinase) association and a 2.5-fold decrease in IRS-1-associated PI3-kinase enzymatic activity ($P < .05$ vs. non-HCV). This was accompanied by a marked reduction in insulin-stimulated Akt phosphorylation without any alterations in mitogen-activated protein kinase (MAPK) phosphorylation. Cellular contents of the hepatic p85 subunit of PI3-kinase were comparable between HCV-infected and non-HCV-infected subjects.

Conclusion

The authors found that (1) HCV infection leads to a postreceptor defect in IRS-1 association with the IR, and (2) Insulin signaling defects in hepatic IRS-1 tyrosine phosphorylation and PI3-kinase association/activation may contribute to insulin resistance, which leads to the development of type 2 diabetes mellitus in patients with HCV infection.



Overweight and Obesity, Hepatic Steatosis, and Progression of Chronic Hepatitis C: A Retrospective Study on a Large Cohort of Patients in the United States

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Source: *Journal of Hepatology*, Vol. 40 (1) 2004 pp 147-154

Introduction

Hepatic steatosis has been associated with chronic hepatitis C (CHC), but its prevalence, risk factors, and clinical significance remain to be determined.

Aims

The present study determined the frequency of, and risk factors for hepatic steatosis and its association with activity and progression of chronic hepatitis C in a large cohort of U.S. patients.

Methods

This is a retrospective study that utilized systematic chart review and statistical analyses to investigate 324 U.S. patients with chronic hepatitis from a university medical center and a regional VA medical center.

Results

The frequency of hepatic steatosis was 66.0%. We demonstrated that not only being obese, but also overweight (i.e. body mass index 25 kg/m^2) was independently associated with hepatic steatosis. In our cohort of patients with chronic hepatitis C, hepatic steatosis, especially grade II/III steatosis was significantly associated with elevated aspartate aminotransferase at entry, persistently elevated alanine aminotransferase, and stage III/IV fibrosis. Grade II/III steatosis, was significantly associated with a higher histology activity index as well. Multivariate analysis indicated that steatosis, especially grade II/III steatosis, was independently associated with stage III/IV fibrosis.

Conclusion

The authors concluded that being overweight/obese serves as an independent risk factor for hepatic steatosis in U.S. patients with chronic hepatitis C. Steatosis accelerates activity and progression of chronic hepatitis C, and is independently associated with stage III/IV hepatic fibrosis in these patients.

Once-Weekly Epoetin Alfa Improves Anemia and Facilitates Maintenance of Ribavirin Dosing in Hepatitis C Virus–Infected Patients Receiving Ribavirin plus Interferon Alfa



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Source: *Am J Gastroenterol* 2003;98

Introduction

Interferon and ribavirin are associated with decreased Hb levels, which can result in anemia. Approximately 26% of HCV-infected patients receiving standard IFN monotherapy experience decreases in Hb levels of 2 g/dl or more. Ribavirin causes a dose-dependent, reversible hemolytic anemia in most patients. Combination therapy with standard interferon plus ribavirin therapy has been associated with severe decreases in Hb levels, to less than 10 g/dl in 8% to 9% of patients.

The standard of care for the management of ribavirin/interferon associated anemia has been to dose reduce ribavirin. However, recent data suggest that lower doses of ribavirin decrease the likelihood of a sustained virological response.

Objective

The aim of this study was to determine the efficacy of epoetin alfa in alleviating anemia and minimizing ribavirin (RBV) dose reductions in patients with chronic hepatitis C virus (HCV) infection receiving combination ribavirin/interferon alfa (IFN) therapy.

Methods

HCV-infected patients who had Hb levels of 12 g/dl or less during the first 24 weeks of combination RBV/IFN therapy (n = 64) were randomized to treatment with epoetin alfa (40,000 units) *s.c. q.w.* or to standard of care (SOC) for anemia management (ribavirin dose reduction or discontinuation, transfusions). Primary and secondary efficacy endpoints were changes in Hb level and ribavirin dosage, respectively, from baseline to week 16 of epoetin alfa therapy.

Results

Based on intent-to-treat analysis, the mean changes from baseline Hb levels at week 16 were ± 2.8 g/dl for epoetin alfa *versus* ± 0.4 g/dl for SOC ($p < 0.0001$), and the mean changes in ribavirin dosage were -34 mg/day for epoetin alfa *versus* -146 mg/day ($p = 0.060$) for SOC. The mean Hb level at week 16 in the epoetin alfa group (13.8 g/dl) was significantly ($p < 0.0001$) higher than that of the SOC group (11.4 g/dl).

At week 4 and subsequently, significantly more patients in the epoetin alfa group did not have ribavirin dosage reductions ($p < 0.011$).

At study end, 83% of epoetin alfa-treated patients maintained ribavirin dosages of at least 800 mg/day, compared with 54% of patients receiving SOC ($p < 0.022$). Epoetin alfa was well tolerated.



Conclusion

In anemic HCV-infected patients treated with ribavirin/interferon, epoetin alfa increases Hb levels and maintains RBV dosing. Based on these results, epoetin alfa seems to be promising in the treatment of HCV treatment-related anemia. Further research is warranted to determine the potential impact on outcomes, including quality of life and sustained viral response rate.

High Body Mass Index Is an Independent Risk Factor for Nonresponse to Antiviral Treatment in Chronic Hepatitis C

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Source: *Hepatology*, Vol. 38, No3, 2003

Introduction

Several factors have been shown to influence response to interferon/ribavirin therapy. Some studies have found that in patients with chronic hepatitis C, the degree of hepatic steatosis and fibrosis correlate with body mass index (BMI) and reduce the rate of sustained virological response to anti-viral therapy.

Aim

The aim of this study was to determine if body mass index (BMI) was an independent predictor of response to antiviral treatment in patients with chronic hepatitis C.

Methods

A retrospective review was performed of all patients at a single center with chronic hepatitis C treated with antiviral medication from 1989 to 2000. A sustained response was defined as either negative hepatitis C virus (HCV) RNA by polymerase chain reaction and/or normal alanine aminotransferase (ALT) level (only in those treated before availability of HCV RNA testing) 6 months following completion of therapy.

All patients were classified into one of 3 groups according to BMI:

1. Normal, $<25 \text{ kg/m}^2$ overweight,
2. $25\text{-}30 \text{ kg/m}^2$ obese,
3. $>30 \text{ kg/m}^2$

A total of 253 patients were treated with either interferon (IFN) monotherapy or interferon in combination with ribavirin. Patients were excluded if predetermined clinical characteristics were unavailable.

Results

Using logistic regression, and after adjusting for the examined variables (age, sex, history of alcohol consumption $>50 \text{ g/d}$, cirrhosis on pretreatment biopsy, and BMI), likelihood ratio tests showed significant differences in response to treatment according to BMI group ($P = .01$), genotype ($P < .01$), and cirrhosis ($P < .01$).

Those with genotypes 2 or 3 had an odds ratio (OR) for success of 11.7 compared with those with genotype 1, cirrhotic patients had an OR of 0.15 compared with noncirrhotic



patients, and obese patients had an OR of 0.23 compared with normal and overweight patients.

Hepatic steatosis was not an independent risk factor for response to antiviral treatment.

Conclusion

The authors concluded that obesity, only when defined as a BMI greater than 30 kg/m² is an independent (of genotype and cirrhosis) negative predictor of response to hepatitis C treatment.

Early Virologic Response to Treatment with Peginterferon Alfa-2b plus Ribavirin in Patients with Chronic Hepatitis C

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Source: *Hepatology* 2003; 38: 645-652

Introduction

Interferon-based regimens for the treatment of chronic hepatitis C have become increasingly effective and are able to eradicate virus in more than one half of cases. Early identification of patients who will not respond is desirable because treatment might be stopped, thereby avoiding the expense and inconvenience of unnecessary therapy.

Objective

We examined the accuracy of different degrees of viral inhibition during the early weeks of treatment early virologic response (EVR) with pegylated interferon alfa-2b and ribavirin (PEG/R) in identifying patients who would not respond to therapy. The best definition of early virologic response was a reduction in hepatitis C virus (HCV) RNA by at least 2 logs after the first 12 weeks of treatment compared with baseline.

Results

Between 69% and 76% of patients achieved this threshold, depending on the treatment regimen, and sustained virologic response (SVR) occurred in 67% to 80% of these patients. Patients who did not reach early virologic response did not respond to further therapy.

If treatment had been stopped in patients without early virologic response, drug costs would have been reduced by more than 20%.

Conclusion

The authors concluded that early confirmation of viral reduction following initiation of anti-viral therapy for chronic hepatitis C is worthwhile. It provides a goal to motivate adherence during the first months of therapy and a milepost at which to reassess the need for continued treatment. Most patients who are able to complete the first 12 weeks of therapy achieve early virologic response and have a high probability of a sustained virologic response. Patients who fail to achieve an early virologic response will not clear



virus even if an additional 9 months of therapy is received. Therapy can be confidently discontinued in those cases.

Single-Dose Pharmacokinetics and Tolerability of Pegylated interferon- α 2b in Young and Elderly Healthy Subjects

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Source: British Journal of Clinical Pharmacology 2003;56:131-134

Introduction

A sizeable minority of patients infected with hepatitis C are of an advanced age, which could potentially alter drug disposition.

Objective

The objective of this study was to determine the effect of increasing age on the pharmacokinetics of PEG-Intron.

Methods

In this parallel design study, a single 1 μ g PEG-Intron dose was given subcutaneously to 24 subjects in the age groups 20-45, 65-69, 70-74 and 75- 80 years ($n = 6$ /group). Blood sampling and tolerability assessments were performed up to 168h post dose.

Results

The pharmacokinetic parameters were similar in all age groups. The elderly to young subject ratios for C_{\max} were 91.1, 79.5, and 107% for the 65-69 years, 70-74 years and 75-80 years groups, respectively.

The corresponding values for AUC and CL/F were 111, 102 and 108%, and 82.5, 95.8 and 86.4%, respectively. Mean differences from the 20 to 45 years group and the 65-69 years, 70-74 years and 75-80 years groups for PEG-Intron Vd/F were 108, 128 and 104% respectively.

None of these differences was statistically significant based on ANOVA. Results from a Dunnett's test (as post hoc assessment) confirmed that the pharmacokinetic parameters of Group II, Group III or Group IV were not different from those of Group I. Almost all (23/24; 96%) subjects reported typical interferon α side-effects (flu-like symptoms, headache). One elderly patient had a myocardial infarction 12 h postdose, but recovered fully.

Conclusions

The authors concluded that there are no pharmacokinetic reasons for initial dose adjustment of PEG-Intron based on age and that age does not affect PEG-Intron clearance. They also noted that further controlled studies involving single or multiple dosing are required to confirm these preliminary findings.



Antiviral Therapy of Patients with Decompensated Cirrhosis to Prevent Recurrence of Hepatitis C after Liver Transplantation

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Journal of Hepatology 39 (2003) 389-396

Background/Aims

After liver transplantation (LT) infection of the graft with the hepatitis C virus (HCV) is almost universal and chronic hepatitis and cirrhosis develop in a significant proportion of patients. One of the possible strategies to prevent HCV infection recurrence is to eradicate HCV before liver transplantation.

Methods

The authors evaluated the efficacy and safety of antiviral therapy to prevent HCV recurrence in 30 HCV-cirrhotic patients awaiting liver transplantation. At the time of inclusion 15 patients were Child-Pugh A and 15 Child-Pugh B/C.

The infecting genotype was 1b in 25 patients. Treatment with interferon α -2b 3 MU/day and ribavirin 800 mg/day was initiated when the expected time for liver transplantation was less than 4 months and continued until liver transplantation. The median duration of treatment was 12 weeks.

Results

Nine patients (30%) achieved a virological response and 21 did not respond to therapy. In nine (43%) of the 21 non-responders viral load decreased ≥ 2 log during treatment. A viral load decrease ≥ 2 log at week 4 of treatment was the strongest predictor of virological response.

All nine virological responders have already undergone liver transplantation; six patients remain free of infection after a median follow-up of 46 weeks and HCV infection recurred in three patients after liver transplantation. In one of these patients HCV-RNA was still detectable in the explanted liver.

Side effects were frequent and dose reduction was necessary in 19 (63%) of the 30 patients; no patient died while on therapy.

Conclusions

The authors concluded that their data supported the utilization of antiviral therapy in HCV-infected patients awaiting liver transplantation as one of the strategies to prevent hepatitis C recurrence after transplantation.



Infection with Chronic Hepatitis C Virus and Liver Transplantation: A Role for Interferon Therapy Before Transplantation

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Source: *Liver Transplantation*, Vol 9, No 9 (September), 2003: pp905-915

Introduction

An analysis of the National Institute of Diabetes and Digestive and Kidney Diseases Liver Transplant Registry data shows that the greater the viral load at the time of transplantation, the more rapidly clinically evident post-transplantation hepatitis C virus (HCV) disease recurs. These data suggest that aggressive pretransplantation treatment of HCV might delay recurrent posttransplantation HCV disease and enhance posttransplantation survival.

Objective/Methods

We have taken an aggressive approach to treating HCV infection pretransplantation with the use of high-dose (5 MU) daily interferon- α 2b in an effort to clear the virus before transplantation.

Patients

A total of 27 patients with HCV-induced cirrhosis were seen and underwent transplantation at Loyola University Medical Center (Maywood, IL) between February 1997 and December 2001. There were 22 men and five women, with a mean age of 56 ± 2 years. The majority had genotype 1 disease (67%). Of the 27 patients, 7 had a baseline platelet count $<50,000/\text{mm}^3$ and were excluded from interferon therapy. The remaining 20 were treated for a mean of 14 ± 2.5 (range, 0.5 to 33.5) months before orthotopic liver transplantation (OLT).

Results

Twelve (60%) responded to the therapy with serologic clearance of HCV before OLT. The mean time from initiation of therapy to the first negative qualitative polymerase chain reaction was 4.5 ± 1.5 (range, 0.5 to 12) months. Four of the 12 patients in whom the virus cleared did not have evidence of HCV recurrence after OLT, representing 20% of those treated and 33% of those who had HCV clearance before OLT. The duration of post-OLT freedom from HCV infection in these individuals has been 33.6 ± 11.3 (range, 0 to 47.4) months.

Conclusion

The authors concluded that with careful supervision cirrhotic patients can tolerate high-dose interferon. In addition, a viral clearance can be achieved in a significant number of cirrhotic patients with high-dose interferon. One third of patients, in whom the HCV cleared before OLT, did not have evidence of disease recurrence after OLT.

It is thus anticipated that with early and aggressive pre-OLT HCV therapy, possibly with the use of pegylated interferon, even better results may be obtained.