Ancillary Study to the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) Trial:

Long-term Follow-up of HALT-C Sustained Virologic Responders

Version Date: June 19, 2008

Study Contacts:

Principal Investigator:
Karen Lindsay, MD, MMM
Keck School of Medicine
University of Southern California
Hepatitis Research and Treatment Center
1640 Marengo Street, Suite 103
Los Angeles, CA 90033
Telephone: (323) 224-5555
FAX: (323) 224-5465
Email: klindsay@usc.edu

Co-Investigators:
Marc Ghany, MD
Liver Diseases Section
Division of Digestive Diseases and Nutrition
National Institute of Diabetes and Digestive and Kidney Diseases
Bldg 10, Room 9B-06
10 Center Drive, MSC 1800
Bethesda, MD 20892-1800
Telephone: (301) 402-5115
FAX: (301) 402-0491
Email: MarcG@bdg10.niddk.nih.gov

Timothy Morgan, MD
VA Medical Center
5901 E. 7th St, 111G
Long Beach, CA 90822
Telephone: (562) 826-5756
FAX: (562) 826-5436
Email: timothy.morgan@va.gov

Anna Lok, MD
University of Michigan
Division of Gastroenterology
1500 E. Medical Center Dr.
3912 Taubman Center
Ann Arbor, MI 48109-0362
Telephone: (734) 936-4780
FAX: (734) 936-7392
Email: aslok@umich.edu

Data Coordinating Center:
Kristin Snow, MSc, ScD
New England Research Institutes, Inc.
9 Galen Street
Watertown, MA -2472
Telephone: (617) 923-7747 ext. 292
FAX: (617) 926-0144
Email: ksnow@neriscience.com

Sponsor:
Division of Digestive Diseases and Nutrition
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health
Department of Health and Human Services
Bethesda, MD

Long-term Follow-up of SVR Patients in the HALT-C Trial
Karen L. Lindsay
FINAL PROTOCOL
June 19, 2008

Study Synopsis:
One hundred eighty subjects who participated in the Lead In phase of the HALT-C trial and experienced an SVR will be contacted for potential entry into this study. After signing an informed consent, the subjects will be given two options for collecting follow-up clinical information since their last study visit. One option will be to be seen at the study site for one visit or, if that is not feasible, data will be collected on their clinical course since their last HALT-C visit by telephone and receipt and review of outside medical records.

Purpose of the study:
To establish a cohort of chronic hepatitis C patients with Ishak stage 3-6 fibrosis who experienced a sustained virologic response (SVR) after peginterferon and ribavirin combination therapy and assess the frequency of clinical outcomes (variceal bleeding, ascites, CTP scores > 7, liver transplant, death) and hepatocellular carcinoma (HCC) and factors associated with these outcomes.

Background/Rationale:
The Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) Trial is a randomized multi-center clinical trial to assess the effects of long-term interferon-alfa 2a therapy on the progression of liver fibrosis and development of decompensated liver disease in patients who have advanced hepatitis C and were non-responders to prior interferon therapy. During the Lead-In phase, subjects were enrolled and treated with a combination of pegylated interferon-alfa 2a (180 mcg/week) and ribavirin (1000-1200 mg/day), and assessed for the presence of serum HCV RNA at week 20 of therapy. Among the Lead-In subjects, 180 subjects developed a virological response at week 20, completed 48 weeks of peginterferon with ribavirin therapy, and continued to have undetectable serum HCV RNA at week 72, twenty four weeks after completing treatment. These subjects completed treatment in 2004, and the last patient completed their week 72 visit in 2004.

Nine (of 11) eligible subjects returned for visits approximately 2-4 years after completing study week 72 visit as participants in the “TMA” ancillary study. Repeat HCV RNA testing in the 9 subjects confirmed long-term HCV RNA negativity [1]. And, although these subjects were several years past their last study visit, the fact that the study staff was able to locate 82% of these subjects eligible for participation in the TMA study is encouraging.

In order to estimate the frequency of clinical outcomes and HCC in the HALT-C SVR cohort, during July 2007, site 19 provided follow-up data on their 35 SVR subjects. One of the 35 had developed HCC, and none of the subjects had developed a clinical outcome. Of the 35 patients, 18 were last seen in 2006-2007, and the remaining patients had last been seen in 2002-2005.

A number of long-term follow-up studies in HCV patients treated with interferon have been reported from Japan[2],[3],[4],[5],[6] The majority of these studies have included patients with mild to advanced hepatic fibrosis, and demonstrated a reduction in the rate of HCC and liver-related death in patients treated with interferon compared to those who were

not. Among the treated patients, a beneficial effect was more pronounced in treated patients who achieved an SVR. Despite SVR, HCC occurred in up to 3.5% of patients.

In large retrospective studies of patients with HCV cirrhosis from Europe[7,8] variable differences in outcome related to interferon therapy were identified, but these studies pre-dated availability of peginterferon therapy and highly sensitive assays for HCV RNA. In a study limited to 80 SVR patients followed for 1 to 7.6 years, 5 with cirrhosis at baseline were described and none of them developed HCC or hepatic decompensation during follow-up[9]. And, a recent report by Maylin[10] describing clinical and histopathologic follow-up in 103 patients up to 18 years after SVR was achieved. Fibrosis stage was described as: improved in 58%, stable in 26%, and deteriorated in 16%, but the stage of fibrosis prior to treatment was not reported in all patients. Regression of cirrhosis occurred in 7/9 patients, but information on clinical outcomes was not reported. In a recent report by Bruno[11] a retrospective database of cirrhotic patients treated with interferon alfa monotherapy was created. During a mean follow-up of 96.1 months (8 years), the incidence rates of liver-related complications, HCC, and liver-related death were significantly lower in the 124 patients with SVR compared to those without SVR. The rates in SVR compared to non-SVR patients were reported as incidence per 100 person-years. SVR vs non-SVR incidence rates were 0 vs 1.88 for liver-related complications, 0.66 vs 2.10 for HCC, and 0.19 vs 1.44 for liver-related death.

Long-term follow-up studies of American patients with SVR are limited. In a study evaluating the long-term outcome of the 10 patients treated at the NIH between 1984 and 1987[12], five patients who experienced SVR underwent liver biopsies which showed improvement and all were asymptomatic.

There are several [13,14,15] five-year follow-up studies of patients from both Europe and the US who achieved SVR with interferon therapy. However, the majority of these patients had been treated in registration trials for interferon or peginterferon with or without ribavirin and did not have advanced hepatic fibrosis. In addition, the primary aim of these studies was to evaluate the likelihood of late virologic relapse. Therefore, clinical data on the rates of hepatic decompensation, HCC or liver transplantation were not reported.

The most comprehensive study of clinical outcomes in patients with hepatitis C and advanced fibrosis was recently published by Veldt[16]. Clinical outcomes were defined as death of any cause, liver failure, and hepatocellular carcinoma. In this retrospective cohort study from 5 hepatology units in Europe and Canada of 142 SVR patients and 337 patients without SVR with a median follow-up of 2.1 years, SVR was associated with a significant reduction in clinical outcomes. This effect was largely attributable to a reduction in liver failure. Baseline features of the patients were not characterized.

The HALT-C cohort of SVR patients are therefore a unique group of American patients with hepatitis C who had more advanced hepatic fibrosis prior to treatment with peginterferon and ribavirin and were followed prospectively. In addition, extensive risk factor and clinical information was collected when they participated in the Lead-In phase. This unique dataset will be very valuable in further evaluating potential risk factors for hepatic decompensation or liver cancer in subjects identified during long-term follow-up.

In addition, by 2008, all subjects will have completed at least 4 years of follow-up since achieving SVR.

Finally, this cohort of subjects who have cleared hepatitis C can serve as a comparator group for the treated and untreated viremic subject groups in the randomized phase of HALT-C trial.

Subject Population, Availability, and Eligibility Criteria:
All 180 patients who developed a virological response at week 20 of the HALT-C Study, completed 48 weeks of peginterferon with ribavirin therapy, and continued to have undetectable serum HCV RNA at week 72, twenty four weeks after completing treatment are eligible for this Ancillary Study. These subjects completed treatment in 2004, and the last patient completed their week 72 visit in 2004.

One hundred eighty subjects treated at the 10 clinical sites met these inclusion criteria:

11 UMass/ UConn	12 SLU	13 MGH	14 UCHSC	15 UCI	16 UTSW	17 USC	18 UMich	19 VCU	20 NIDDK	TOTAL
24 (20/4)	11	8	27	13	17	25	16	35	4	180

Breakdown of 180 patients by fibrosis strata:
- Stage 5/6: 38
- Stage 2-4: 142

Nine (of 11) eligible subjects returned for visits approximately 2-4 years after completing study week 72 visit as participants in the HALT-C "TMA" Ancillary Study. Repeat HCV RNA testing in the 9 subjects confirmed long-term HCV RNA negativity [17]. These 11 patients will also be eligible to participate in this Ancillary Study.

Description of Planned Study Procedures:
1. The Protocol and Informed Consent Form would be submitted at each Clinical Center and the Data Coordinating Center for local IRB approval.
2. Invitation to participate: Patients will be contacted by a staff member from the HALT-C Clinical Center where they received care during the study, and invited to either:
    a. return to the Clinical Center for one follow-up study visit and possible additional blood draw OR
    b. provide consent for follow-up information collected since the date of their Week 72 HALT-C visit; this information will be obtained via telephone interview and medical record abstraction.
3. Protocol visit performed at the HALT-C clinical site:
    a. If the patient agrees to come for a visit at the HALT-C Clinical Center, at the time of the visit:
        i. the purpose of the Study will be explained to the patient, and the patient will be asked to sign an Informed Consent Form. The patient will be given a copy of the signed Informed Consent Form.
        ii. a brief history will be taken.

iii. a physical examination will be performed for detection of ascites and encephalopathy and weight will be measured
iv. blood may be drawn for laboratory tests to include complete blood count, serum creatinine, liver chemistries, prothrombin time, AFP, HCV RNA assay
v. an abdominal ultrasound may be performed for detection of ascites
vi. If applicable, the patient will be asked to sign medical record release form(s) for facilities that provided care for study clinical outcomes since the date of their Week 72 HALT-C visit

b. If any of the study procedures cannot be completed at the time of the visit to the Clinical Center, the patient will be asked to sign medical record release form(s) as applicable. The form will allow the clinical site staff to request retrieval of medical record information related to:
   i. a recent physical exam (weight, detection of ascites and encephalopathy)
   ii. a recent liver imaging test (abdominal ultrasound, MRI, or CT)
   iii. recent laboratory testing (complete blood count, serum creatinine, liver chemistries, prothrombin time, AFP, HCV RNA assay)

4. Protocol visit performed by telephone interview with the subject:
   a. Informed consent: the purpose of the Study will be explained to the patient, and the patient will be mailed an Informed Consent Form. The patient will be asked to sign the Informed Consent Form and mail it back to the Clinical Center. An addressed, stamped return envelope will be provided.
   b. After mail receipt of the signed Informed Consent Form, the patient will be contacted by telephone by the Study Coordinator. The Coordinator will complete the Study Forms.
   c. The patient will be mailed a copy of their signed Informed Consent Form and medical record release forms to be signed. An addressed, stamped return envelope will be provided. This consent form will allow the clinical site staff to request retrieval of medical record information related to:
      i. a recent physical exam (weight, detection of ascites and encephalopathy)
      ii. a recent liver imaging test (abdominal ultrasound, MRI, or CT)
      iii. recent laboratory testing (complete blood count, serum creatinine, liver chemistries, prothrombin time, AFP, HCV RNA assay)
      iv. If applicable, the patient will be asked to sign medical record release form(s) for facilities that provided care for study clinical outcomes since the date of their Week 72 HALT-C visit.

Physical examinations, imaging studies, laboratory testing, and HCV RNA assays would be considered standard of care and conducted through the patient's health care system or Clinical Center funding if available at the Clinical Center. If these procedures cannot be conducted at the Clinical Center, the patient will be asked to sign a release of medical information to collect documentation of the most recent physical examination, imaging study, laboratory testing, and HCV RNA assay from the patient's local health care provider.

Blood samples may be drawn at the clinical center for laboratory testing. No additional blood samples would be collected, shipped, or stored on subjects participating in this ancillary study. Any clinically significant blood tests or ultrasound performed at the clinical center will be reported to the patient.

Clinical outcomes for this study are listed below. Appendices A and B contain outcome definitions.

1. Death from any cause
2. Development of hepatocellular carcinoma (HCC)
3. CTP score of 7 or higher
4. Variceal hemorrhage
5. Ascites
6. Spontaneous bacterial peritonitis
7. Hepatic encephalopathy
8. Liver transplant
9. Presumed Hepatocellular Carcinoma

All clinical outcome events will be reviewed by the HALT-C Outcome Review Board (ORB). Members of the Board include Principal Investigators from the Clinical Centers and the Scientific Officer of the NIDDK. Clinical Centers will submit to the DCC the appropriate forms and source documents. Copies of these documents will be sent to two members of the ORB, and to a third if there is not consensus. Outcomes will be evaluated by the ORB based on pre-determined criteria for each outcome variable.

Data collection:
The following Forms would be completed on each subject who has consented. Site staff will data enter these Forms into the Data Management System.

Form # 701	Study Consent Information	To include information about subjects who could not be located or have died.
Form # 710	Study Visit	To be conducted by telephone or in-person.
Form # 711	Physical Exam	To be conducted at clinical center or completed from medical record review.
Form # 715	Child-Turcotte-Pugh (CTP) score	To be completed from physical exam and laboratory results at clinical center or completed from medical record review.
Form # 722	Liver Scan Results: Ultrasound, MRI, or CT	To be conducted at clinical center or completed from medical record review.
Form # 730	Laboratory Results: Complete Blood Count, Serum Creatinine, Liver Chemistries, Prothrombin Time, Alpha-Feto Protein (AFP), HCV RNA Assays	To be conducted at clinical center or completed from medical record review.

When indicated, the following two forms would also be completed and sent to the DCC. Data entry will be done at the DCC for these two forms.

Form # 763	Clinical Outcome	To be completed for any reported clinical outcome event. See Appendices A and B for definitions of clinical outcomes.
Form #765	Clinical Outcome Review	All clinical outcome events will be reviewed by study investigators. Review information will be recorded on Form #765.

Clinical Center staff will try to locate each eligible patient to determine if they want to participate in the study. According to appropriate regulations, the Clinical Center will attempt to determine the mortality status of any patient not located at their last known address.

Data obtained from these studies may be published, but participating patients will not be individually identified in any publication.

Anticipated results/ Statistical Analysis Plan:

1. Incidence of hepatocellular carcinoma would be less than 5% in these SVR subjects.
2. Incidence of hepatic decompensation, liver transplant, or death due to liver-related causes in SVR subjects would be less than patients who participated in the randomized phase when matched for liver histology.
3. The effect of SVR in reducing the risk of clinical outcomes is greater than the effect of co-morbid conditions

Statistical Analysis Plan:

Comparison Group: All subjects in the HALT-C trial who participated in the Lead-In phase, were treated with peginterferon and ribavirin, had HCV RNA detectable at treatment week 20, and were randomized to the control group (treated group will not be included because they had a significant decrease in ALT and HCV RNA compared to control)

Variables to be included in analyses: Hepatic decompensation variables (CTP score > 7, ascites, variceal bleed, hepatic encephalopathy), liver-related death, non-liver related death, hepatocellular carcinoma, SVR, non-SVR, baseline hepatic steatosis, BMI

Statistical Methods: Kaplan-Meier curves to assess clinical outcomes in SVR vs non-SVR cohorts; Cox regression models to evaluate effects of baseline co-morbid conditions

Risk/Benefit Analysis:
If blood is drawn at the study site, there is potential risk involved in a venipuncture and phlebotomy. Potential benefits to study participation include blood testing which may be conducted at the study site at no cost to the patient.

Definition, monitoring, and reporting of adverse events:

1. Definition
   a. An adverse event is any adverse change from the patient's baseline (pretreatment) condition, including intercurrent illness which occurs during the course of the visit, and for twenty-four hours after the consent form has been signed, whether the event is considered related to a study procedure or not.
   b. A serious adverse event is an untoward medical occurrence that results in any of the following:
      1. Death
      2. Is life threatening (risk of death at the time of the event).
      3. Requires in-patient hospitalization or prolongation of existing hospitalization
      5. Results in persistent or significant disability/incapacity
      6. Congenital abnormality or birth defect

      Important medical events that do not result in one of the events listed above may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

2. The following events are study outcomes and will not be considered to be serious adverse events:
   1. Development of HCC or presumed HCC
   2. A CTP score of 7 or higher
   3. Ascites
   4. Variceal hemorrhage
   5. Hepatic encephalopathy
   6. Spontaneous bacterial peritonitis

3. Data collection procedures for adverse events
   a. For up to 24 hours after an in-person study visit occurs, any adverse event will be recorded in the medical record and submitted to the site's local IRB (see below). Patients will report medical conditions, medical changes, and symptoms that have occurred since the visit.
   b. Patients will be followed for all ongoing unresolved adverse events until they are either resolved, or in the opinion of the Principal Investigator, the patient is medically stable.

4. Reporting procedures
   a. All serious adverse events, for patients will be reported to the site's local IRB within the timeframe required according to local IRB standards.

b. All deaths will be reported to the site's local IRB according to local IRB standards. A death must also be reported in accordance with local law and regulations.

Data management and quality control procedures:
Clinical Center staff will use the HALT-C web-based data entry system developed and maintained at the DCC at New England Research Institutes (NERI). This system uses NERI's Advanced Data Entry and Protocol Management System (ADEPT). Clinical Center staff will use this system for data entry of study forms. Information entered into the data entry system will be by patient study ID; names will not be linked with patient data in the database. Clinical centers will maintain records linking the patient name with the ID assigned for this study in locked files.

The data entry system will include context specific help, automatic skip patterns, range checks, and intra- and inter-form checks of the data as it is being entered.

The system will produce a visit control sheet that will list all of the forms and procedures for a scheduled visit.

The data sets created by ADEPT will be converted to SAS data sets at the DCC. Additional data editing will be performed at the DCC using SAS. Outliers will be identified using predetermined limits and graphical methods. These edits will also compare patient data across forms. Edit messages will be sent to the Clinical Centers for clarification as needed.

Limitations of the study:
The number of subjects who complete visits in the study may be insufficient to draw conclusions from the data.

APPENDICES

A. Definitions

Ascites: Any abdominal fluid which is:
1. Mild, moderate or marked on ultrasound; or
2. Progressive on serial physical examinations; or
3. Requires diuretic therapy.

To meet the definition of ascites, abdominal fluid that is "mild" ("barely detectable") on physical examination requires ultrasound confirmation that is "mild", "moderate" or "marked" ascites. Ultrasound reports of minimal fluid around the liver do not meet the definition.

Hepatic encephalopathy: Any mental status alteration which is deemed by the investigator to be due to portosystemic encephalopathy, whether occurring during a provoked episode (GI bleeding, diuretics, usual sedative doses), or spontaneously (without apparent cause).

Hepatocellular carcinoma: A diagnosis of HCC will be based on <u>either</u>
1. Histology showing HCC (from a biopsy, surgery, or autopsy) <u>or</u>
2. A new hepatic defect on imaging with an AFP rising to > 1,000 ng/ml.

Presumed Hepatocellular Carcinoma: Presumed HCC will be considered when histology is not available and AFP is <1000 ng/ml, if:
1. A new hepatic lesion is shown on ultrasound and one additional imaging which shows a hepatic lesion with characteristics of HCC.
2. AFP >ULN and two imaging studies show a hepatic lesion with characteristics of HCC.
3. A progressively enlarging hepatic lesion starting as a new defect eventually resulting in the death of a patient.
4. A new hepatic defect with at least 1 characteristic scan and one of the following:
   a. Increase in size over time (doubling in diameter or tripling in diameter if the initial size <1 cm when first discovered) or
   b. An increasing AFP (values 3 months before or after the discovery of the defect by scanning) eventually rising to a level of >200 ng/ml and more than tripling the mean baseline value.

Images may include:
1. MRI
2. triphasic CT
3. angiography (angiography taken prior to intra-arterial chemo-embolization may be used for this purpose if images are taken and reported prior to therapeutic intervention)
4. lipiodol scan

5. liver spleen scan with gallium

Characteristics of HCC include:

1. Hypervascularity
2. Arterial to portal vein shunts
3. Portal vein thrombosis near the defect
4. Tumor in the portal vein.

Spontaneous bacterial peritonitis: Any episode of spontaneous ascitic infection diagnosed on the basis of elevated neutrophil count (> 250/ml) in paracentesis fluid or positive bacterial cultures and clinical diagnosis in the absence of WBC availability.

Variceal hemorrhage: A gastrointestinal hemorrhage which is believed by the investigator to be due to bleeding esophageal or gastric varices. In general, an endoscopy will have been performed and will have revealed either direct evidence of variceal bleeding (bleeding varix, red wale sign) or historical evidence for significant upper gastro-intestinal bleeding plus upper endoscopy revealing moderate varices and no other site of bleeding is identified.

B. Child-Turcotte-Pugh Score for Grading Severity of Liver Disease

Modified Child-Turcotte-Pugh Score				
		# of points		
Variable	**Units**	**1**	**2**	**3**
Serum albumin	(g/dL)	>3.5	2.8-3.5	<2.8
Serum total bilirubin (No Gilbert's Syndrome; No hemolytic diseases; Not receiving ribavirin)	(mg/dL)	<2.0	2.0-3.0	>3.0
Serum total bilirubin (In presence of Gilbert's Syndrome, a hemolytic disorder [e.g., patients receiving ribavirin]) ‡	(mg/dL)	<4.0	4.0-7.0	>7.0
Prothrombin Time	(INR)	<1.7	1.7-2.3	>2.3
Ascites		None	mild*	severe+
Encephalopathy		None	mild*	severe+

*Mild means readily controlled by standard medical therapies.
+Severe means difficult to control or uncontrollable by optimal, maximally tolerated medical therapies.

Prothrombin time results should be reported and used for calculations only as International Normalized Ratios (INR), because of variations in methods used and reference ranges for controls (expressed in seconds).

‡ Note that if, in the opinion of the investigator, the patient has Gilbert's syndrome or a hemolytic disorder (e.g., patients receiving ribavirin) the level of the serum total bilirubin may be increased to as high as 3.99 mg/dL without considering the total bilirubin to be sufficiently elevated for the patient to receive a score of 2 in the CTP scoring system.

The score is calculated as the sum of the scores for albumin, bilirubin, prothrombin time, ascites and encephalopathy (range 5-15). Class A is defined as 5-6, class B 7-9 and class C 10-15.

Scoring of Prothrombin Time:
If the prothrombin time cannot be completed or would be invalid because the patient is on anticoagulant therapy, a default score of "1" should be recorded.

Scoring of Ascites:
If data of an imaging study is available, then the determination of ascites should be based on that imaging study. If a medical record of a recent abdominal imaging is not available, the PI should determine whether there is a history consistent with ascites.

If the patient is not being seen at the study site and the visit is completed by review of the medical record, and the medical record has no recent abdominal imaging, the PI should determine whether there is history consistent with ascites.

Scoring of Hepatic Encephalopathy:
If the patient is not being seen at the study site and the visit is completed by review of the medical record, and the medical record has no recent determination of whether the patient presented with encephalopathy, the PI should determine whether there is history consistent with encephalopathy.

References

[1] Morishima CM, Morgan T, Everhart JE, et al. HCV RNA Detection by TMA during the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) Trial. Hepatology 2006; 44:360-367.
[2] Ikeda K, Saitoh S, Arase Y, et al. Effect of interferon therapy on hepatocellular carcinoma in patients with chronic hepatitis type C : a long-term observation study of 1,643 patients using statistical bias correction with proportional hazard analysis. Hepatology 1999; 20: 1124-1130.
[3] Yoshida H, Shiratori Y, Moriyama M, Arakawa Y, et al. Interferon therapy reduces the risk for hepatocellular carcinoma: national surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. Ann Intern Med 1999;131:174-181.
[4] Imazeki F, Yokosuka O, Fukai K and Saisho H. Favorable prognosis of chronic hepatitis C after interferon therapy by long-term cohort study. Hepatology 2003;38:493-502.
[5] Kobayashi S, Enomoto M, Tamori A, et al. The incidence of hepatocellular carcinoma in patients with chronic hepatitis C who achieved sustained virological response to interferon therapy. J Hepatology 2006; Suppl 2; 44:S219.
[6] Shindo M, Hamada K, Oda Y, Okuno T. Long-term follow-up study of sustained biochemical responders with interferon therapy. Heptology 2001; 33:1299-1302.
[7] Fattovich G, Giustina G, Degos F et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. Gastroenterology 1997; 112: 463-472.
[8] Serfaty L, Aumaitre H, Chazouilleres O et al. Determinants of outcome of compensated hepatitis C virus-related cirrhosis. Hepatology 1998;27:1435-1440.
[9] Marcellin P, Boyer N, Gervais A, et al. Long-term histologic improvement and loss of detectable intrahepatic HCV RNA in patients with chronic hepatitis C and sustained response to interferon-alfa therapy. Ann Int Med 1997; 127:875-881.
[10] Maylin S, Martinot-Peignoux M, Boyer N, et al. Sustained virological response is associated with eradication of hepatitis C virus and fibrosis regression in patients treated for chronic hepatitis C. Hepatology 2006;44:695A.
[11] Bruno S, Stroffolini T, Colombo M et al. Sustained virological response to interferon-alfa is associated with improved outcome in HCV-related cirrhosis: a retrospective study. Hepatology 2007:45:579-587.
[12] Lau D T-Y, Kleiner DE, Ghany MG et al. 10-year follow-up after interferon-alfa therapy for chronic hepatitis C. Hepatology 1998;28:1121-1127.
[13] McHutchison JG, Shiffman ML, Gordon SC, et al. Sustained virologic response (SVR) to interferon-alpha-2b +/- ribavirin therapy at 6 months reliably predicts long-term clearance of HCV at 5-year follow-up. J Hepatology 2006; Suppl 2; 44:S275.
[14] Swain MG, Lai M-Y, Shiffman ML, et al. EASL 2007
[15] Manns M, Lindsay KL, Gordon SC, et al. EASL 2007
[16] Veldt BJ, Heathcote EJ, Wedemeyer H, Reichen J, Hofmann WP, Zeuzem S, Manns MP, Hansen BE, Schalm SW, Janssen HLA. Annals Int Med 2007; 147:677-684.
[17] Morishima CM, Morgan T, Everhart JE, et al. HCV RNA Detection by TMA during the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) Trial. Hepatology 2006; 44:360-367.