From Diagnosis to Treatment: The Full Spectrum of Care in Hepatitis C

A CME Satellite Symposium presented during the 54th AASLD Annual Meeting
This program is not affiliated with AASLD

Syllabus
Monday, October 27, 2003
Boston, Massachusetts
From Diagnosis to Treatment: The Full Spectrum of Care in Hepatitis C

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DEVELOPMENT FACULTY

Robert G. Gish, MD, is medical director of the Liver Transplant Program at California Pacific Medical Center in San Francisco. He also serves as associate clinical professor of medicine at both the University of Nevada, Reno, and the University of California, San Francisco. Dr. Gish is a faculty member at the Merced Community Hospital, Family Medicine Program, University of California, Davis, in Sacramento. He is currently president of the Pacific Hepatology and Gastroenterology Medical Group. In addition to authoring numerous original articles that have appeared in publications such as Liver Transplantation, Hepatology, and The New England Journal of Medicine, Dr. Gish has lectured nationally and internationally on a wide range of topics, including management of chronic liver disease and liver transplantation. In 2002 he was awarded the Salute to Excellence from the American Liver Foundation.

Ira M. Jacobson, MD, is chief of the Division of Gastroenterology and Hepatology at Weill Medical College of Cornell University, where he also holds the positions of Vincent Astor Professor of Clinical Medicine and medical director of the Center for the Study of Hepatitis C at Rockefeller and Cornell. Dr. Jacobson is an attending physician at New York Presbyterian Hospital in New York. He received his MD degree in 1979 from Columbia University College of Physicians and Surgeons. He has authored or coauthored numerous articles that have appeared in publications that include The New England Journal of Medicine, Journal of the American Medical Association, The Lancet, and American Journal of Gastroenterology. Dr. Jacobson is editor of two books on endoscopic retrograde cholangiopancreatography (ERCP) and is currently principal investigator in several ongoing research projects in the field of hepatitis C. He is the recipient of many honors and awards including the Robert Loeb Award for Excellence in Clinical Medicine from Columbia University. Dr. Jacobson is a past president of the New York Society for Gastrointestinal Endoscopy and the New York Gastroenterological Association.

John G. McHutchison, MD, is director of Gastroenterology/Hepatology Research at Duke Clinical Research Institute, Duke University Medical Center, Durham, North Carolina. He has published worldwide in the field of liver diseases, and is the author of numerous articles and book chapters on chronic hepatitis C infection. He also serves on the editorial board for Viral Hepatitis Review and Hepatology. Dr. McHutchison is active as a reviewer for The New England Journal of Medicine, The Lancet, Gastroenterology, Journal of Hepatology, Journal of Infectious Diseases, Journal of Gastroenterology and Hepatology, and American Journal of Gastroenterology. In addition, he is a fellow of the Royal Australian College of Physicians, as well as a member of several professional organizations, including the American Association for the Study of Liver Diseases and the American Gastroenterology Association. He received his MD degree in 1981 from the University of Melbourne, Australia, and completed his internship, residency, and gastroenterology fellowship at the Royal Melbourne Hospital. Dr. McHutchison then completed an advanced fellowship in hepatology at the University of Southern California, Los Angeles. For the past 10 years, he served as medical director of Liver Transplantation and head of the Hepatitis Study section at Scripps Clinic and Research Foundation in La Jolla, California.

Mark S. Sulkowski, MD, is assistant professor of medicine in the Division of Infectious Diseases, and medical director of the Viral Hepatitis Center, at Johns Hopkins University School of Medicine in Baltimore, Maryland. Dr. Sulkowski received his MD degree in 1992 from Temple University School of Medicine in Philadelphia, Pennsylvania. His professional experience includes serving as attending physician for the Infectious Diseases Consult Service at Union Memorial Hospital in Baltimore (1996–1998). In 1999 he was appointed vice president and director of Clinical Research at the Hepatitis Resource Network in Tacoma, Washington. Dr. Sulkowski was named coinvestigator (2001) to the Johns Hopkins University Adult AIDS Clinical Trials Unit. He is presently a member of the Adult AIDS Clinical Trials Group, Liver Diseases Subcommittee; the Johns Hopkins General Clinical Research Center, Protocol Review Committee; and the Hepatitis Advisory Group, Adult AIDS Clinical Trials Group. A leading contributor to the professional literature, Dr. Sulkowski is author or coauthor of numerous peer reviewed scientific articles in journals including Clinical Infectious Diseases, American Journal of Gastroenterology, and The New England Journal of Medicine.
**TARGET AUDIENCE**

This activity is designed for gastroenterologists and hepatology health professionals who treat patients with hepatitis C.

**ACTIVITY GOAL**

The goal of this activity is to discuss recent advances in hepatitis C and to develop strategies to improve SVR and treatment adherence in infected patients.

**LEARNING OBJECTIVES**

After participating in this activity, the participant should be able to:

- Describe the current standard of care and emerging therapeutic approaches for treatment of HCV infection.
- Compare various ultrasensitive tests and their applications for HCV diagnosis and treatment monitoring.
- Discuss the role of biochemical markers in predicting liver fibrosis and activity.
- Manage side effects to improve treatment adherence.
- Develop management strategies using currently available therapies to maximize outcomes for individual patients.

This independent CME activity is supported by unrestricted educational grants from

- **AMGEN**
- Bayer HealthCare Diagnostics Division
- Prometheus Laboratories
- **HEPATITIS**
From Diagnosis to Treatment: The Full Spectrum of Care in Hepatitis C

Dear Colleague:

From Diagnosis to Treatment: The Full Spectrum of Care in Hepatitis C builds on your current knowledge of diagnosis, treatment, and monitoring of hepatitis C to explore the latest advances and nuances of care. Key topics will focus on:

• Advantages and limitations of specific HCV RNA tests.
• How and when these tests are best used to monitor treatment response.
• Selecting and tailoring available treatment regimens to enhance the likelihood of sustained response and to limit disease progression.
• Improving adherence through aggressive side effect management.
• New biochemical markers that may provide a convenient and minimally invasive means of monitoring liver fibrogenesis.

The format of From Diagnosis to Treatment: The Full Spectrum of Care in Hepatitis C is interactive, designed to stimulate participants to ask questions about emerging strategies for hepatitis C treatment. A discussion of case studies will focus on key clinical issues and unique management challenges. This symposium provides a comprehensive conceptual framework for innovative tests and treatments that will translate into practical clinical skills.

I thank you for joining us for this exciting and informative event.

Sincerely,

John G. McHutchison, MD
Activity Chair
Over the past decade, we have made significant enhancements in the care of our patients with hepatitis C virus (HCV) infection. We now have a greater understanding of the epidemiology and natural history of this disease, as well as the contribution of alcohol to disease progression. Enhanced testing methods for both diagnosis and monitoring of treatment are available. Some of the most important advances include improved therapeutics and strategies for individualizing their use and enhancing treatment outcomes.

Our current most effective treatment regimen combines peginterferon and ribavirin. Pegylated interferons and their improved pharmacokinetic properties allow more convenient once-weekly dosing than standard interferons, with few additional side effects. With peginterferon/ribavirin combination therapy, we can achieve a sustained response, long-term eradication of the virus, and histologic benefits in more than 50% of patients. We have learned that higher doses of ribavirin and longer durations of treatment enhance response rates for patients infected with HCV genotype 1, the most common and difficult-to-treat genotype. With new, highly sensitive virologic tests, we can now accurately predict response and lack of response to therapy by measuring whether a patient has had a 2-log reduction in HCV RNA at week 12 of therapy. Finally, we have recognized the important correlation between adherence and response, and have refined approaches to side-effect management that allow us to maintain patients on therapeutic doses, thereby enhancing their ability to respond.

A number of critical issues need to be addressed as we move forward in caring for our patients with hepatitis C. Despite important treatment advances, not all patients are candidates for therapy and many patients do not respond to treatment, so further therapeutic developments are needed. Many questions remain regarding optimal treatment regimens for various populations, and individualizing therapy will be important. Can we treat patients with HCV genotype 2 or 3 infection with lower doses of our current drugs or
for a shorter duration of time? How can we accurately predict relapse during therapy so that these patients may be provided alternative therapies or a reinforced regimen? What preemptive strategies should routinely be considered to promote adherence? With the introduction of noninvasive markers of fibrosis, what is the role of liver biopsy in staging liver disease associated with hepatitis C? Who should be considered for maintenance therapy to prevent progression of fibrosis?

Finally, new or novel agents that act via inhibition of HCV-specific enzymes, or other molecular-based approaches will become a part of our regimens within the next decade. These regimens will need careful evaluation to determine how and when they should be used and in which patient populations, and to determine their resistance profiles, efficacy, safety, and tolerability. Given current and impending treatment advances, the future will certainly be bright and positive for the many patients infected with hepatitis C.
Themes Over The Past 12 Years...

- Viral discovery
- Diagnostic tests
- Epidemiology
- Natural history
- Role of alcohol
- Interferon therapy
- Addition of ribavirin
- Pegylation
- Focus on fibrosis
- Potential for maintenance therapy
- Strategies to ensure adherence

Key Developments

Molecular Biology and Pathobiology of HCV

- HCV heterogeneity identified
- Genomic organization elucidated
- Gene products and functions characterized
- New diagnostic tools developed
Yesterday, Today, and Tomorrow:
The Evolution of Care for Patients with Hepatitis C
John G. McHutchison, MD

Notes to Myself for Questions at the Meeting:

Ranges of Linear Quantification of HCV RNA Assays (IU/mL)

Variety of Natural Histories
Factors That May Influence Outcome

From Diagnosis to Treatment: The Full Spectrum of Care in Hepatitis C
The Decision to Treat HCV Infection

- Complex
- Controversial
- Multifactorial
  - Host
    - Severity of disease
    - Co-morbid conditions
  - Viral
    - Genotype
  - Therapy
    - Efficacy
    - Side effects
    - Cost
    - Staff

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Yesterday, Today, and Tomorrow:
The Evolution of Care for Patients with Hepatitis C

John G. McHutchison, MD

Notes to Myself for Questions at the Meeting:

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Treatment 2002
Liver Biopsy

- Is generally advisable
- Should not be mandatory
- Aids in decision-making process before and during therapy
  - Contextual disease information
  - Natural history of disease
  - Treatment response
  - Risks and benefits
  - Changing landscape—now
Yesterday, Today, and Tomorrow: The Evolution of Care for Patients with Hepatitis C

John G. McHutchison, MD

Notes to Myself for Questions at the Meeting:

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From Diagnosis to Treatment: The Full Spectrum of Care in Hepatitis C
Yesterday, Today, and Tomorrow:
The Evolution of Care for Patients with Hepatitis C
John G. McHutchison, MD

Notes to Myself for Questions at the Meeting:

Enhancing Response

Future Initiatives
From Diagnosis to Treatment: The Full Spectrum of Care in Hepatitis C

Yesterday, Today, and Tomorrow:
The Evolution of Care for Patients with Hepatitis C

John G. McHutchison, MD

Notes to Myself for Questions at the Meeting:

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Ideal Therapy

- Highly effective
- Orally bioavailable
- Suitable for majority of patients
- Few side effects
- Inexpensive/cost-effective

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Themes Over The Next 10 Years…

- Prediction of relapse
- Prediction of disease progression
- Enhancement of adherence
- New drug development
- Multidrug regimens
- Prevention of resistance
- Replacement of liver biopsy
- Individualized care
- Maintenance strategies
- Prevention of recurrent disease posttransplant
- Effective vaccination

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Slide 11

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Slide 12

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Management of hepatitis C has become increasingly sophisticated in recent years and is now tailored to individual patients based on viral levels before and during therapy, as well as on hepatitis C virus (HCV) genotype. Therefore, it is important to optimize the use of our best molecular tests, as well as currently available treatments.

Measurements of HCV RNA allow physicians to monitor and predict response, and to modify the treatment approach accordingly. The primary goal of treatment is sustained virologic response (SVR), defined as the absence of detectable HCV RNA in the serum by a qualitative HCV RNA assay with a lower limit of detection of ≤50 IU/mL at 24 weeks after the end of treatment. With peginterferon/ribavirin combination therapy, SVR can be achieved by 42% to 51% of patients with genotype 1 and by 73% to 82% of patients with genotypes 2 and 3. Early virologic response (EVR)—defined as undetectable HCV RNA or a ≥2-log10 decrease in HCV RNA after 12 weeks of therapy—is predictive of SVR and is recommended as a routine part of monitoring patients with genotype 1. In patients infected with genotype 1 who demonstrate EVR, adherence to treatment can have a substantial impact on the likelihood of achieving SVR. Thus, educating patients about EVR may provide a major motivating factor to continue therapy. Patients who fail to achieve EVR at 12 weeks of treatment have only a small chance of subsequently achieving SVR even with continued therapy for 48 weeks. In such cases, the clinical decision to maintain therapy beyond 12 weeks should take into account other factors (eg, patient tolerance, stabilization of fibrosis progression in patients with advanced histology). In addition to pretreatment genotype determination and early testing of viral response during treatment, a follow-up qualitative test should be performed, particularly at the end of treatment, to confirm the absence of active HCV replication. Until further studies determine whether SVRs are sustained over the long term following successful antiviral treatment, periodic measurements of HCV RNA may need to be performed.

A number of HCV RNA assays have been developed, and characteristics vary with regard to dynamic range of HCV RNA detection as well as sensitivity and specificity. In general, qualitative assays have a lower range of detection than quantitative assays; however, quantitation is important in making early
determinations of response. Accurate assessment of baseline viral load and determination of logarithmic decreases may require an assay with a high detection limit. The bDNA assay has a greater ability to detect high viral loads than does polymerase chain reaction (PCR). Detection of especially low levels of virus is important in determining response and relapse. A recently developed transcription-mediated amplification (TMA) RNA assay has a lower limit of detection of approximately 5 to 10 IU/mL and may prove to be especially useful at the end of treatment in helping to define long-term response and in long-term management strategies and decisions.

There are six distinct genotypes, classified by percent homology (<70% = different genotypes). Genotype testing is performed at baseline because determinations influence treatment decisions. Approximately 70% to 75% of HCV-infected individuals in the United States are infected with genotype 1, which is associated with a lower rate of response to treatment; the remainder are infected primarily with genotypes 2 and 3. In patients with genotype 1, peginterferon/ribavirin regimens are more effective than standard interferon/ribavirin regimens, but among patients with genotype 2 or 3, SVR rates are comparable to either peginterferon/ribavirin or standard interferon/ribavirin regimens. For patients with genotype 1 infection, 48 weeks of treatment and standard doses of ribavirin (1000–1200 mg/d) are necessary, while 24 weeks of treatment and a ribavirin dose of 800 mg/d appear to be sufficient for patients with genotype 2 or 3. Because of the high response rates in patients with genotypes 2 and 3, early HCV RNA testing in these patients is not necessary.

Genotyping is performed by either reverse-hybridization line probe assay (INNO-LiPA), direct sequencing test (TruGene), or restriction fragment length polymorphism (RFLP) assay. These assays have been found to have a high degree of concordance and reliability. Among qualitative assays, the TMA assay has equivalent detection of all genotypes. The PCR assay has similar detection of genotypes except for genotype 5. Among quantitative assays, the bDNA assay quantifies non-1 genotypes within 1.5-fold of genotype 1, and levels of detection of non-1 genotypes are within 1.3-fold of genotype 1. With the PCR assay, measured values from various genotypes could differ from expected values by 0.51 log10.

In conclusion, determinations of HCV RNA and genotype are clinically important and help determine management strategy. Technologic advances have been made in the assays used to make these determinations, and consideration should be given to the advantages and limitations of these assays when measurements and decisions are made.

Suggested Readings
Molecular Testing for HCV RNA in Monitoring Therapy: PEG IFN + RBV

Testing Algorithm for Naive Patients

Genotype 1
- 48 weeks of therapy

Genotype non-1
- 24 weeks of therapy

Consider stopping therapy

6 months follow-up qualitative test

End-of-treatment qualitative test

Therapeutic response
- HCV RNA (+) relapser
- HCV RNA (-) sustained responder
- <2 log drop
- >2 log drop

Baseline Quantitative Test and Genotyping Test

Week 12 Quantitative Test

<2 log drop

Notes to Myself for Questions at the Meeting:

Ranges of HCV RNA Assays

**QUALITATIVE**
- NGI (PCR)
- Roche (PCR)
- Bayer (TMA)

**QUANTITATIVE**
- NGI (PCR)
- Roche (PCR)
- Bayer (bDNA 3.0)
- Quest TMA Quantitative
- Quest Real-Time PCR
- Roche TaqMan ASR

HCV RNA Concentration in log IU/mL

Comparison of Amplification Methods

<table>
<thead>
<tr>
<th>Method</th>
<th>Dynamic range</th>
<th>Linearity</th>
<th>Specificity</th>
<th>Precision</th>
<th>Genotype quantification</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCR</td>
<td>615–7,700,000 IU/mL</td>
<td>&lt;0.1 log_{10}</td>
<td>98.8% at detection cutoff</td>
<td>16.4%–32.4% CV</td>
<td>Non-1 genotypes quantified within 1.5-fold of genotype 1</td>
</tr>
<tr>
<td>TMA</td>
<td>600–500,000 IU/mL</td>
<td>&lt;0.3 log_{10}</td>
<td>100% at detection cutoff</td>
<td>~18%–39% CV</td>
<td>Measured values from various genotypes could differ from expected values</td>
</tr>
<tr>
<td>bDNA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


HCV Quantitative Assay Characteristics

<table>
<thead>
<tr>
<th>Assay</th>
<th>Dynamic range</th>
<th>Linearity</th>
<th>Specificity</th>
<th>Precision</th>
<th>Genotype quantification</th>
</tr>
</thead>
<tbody>
<tr>
<td>VERSANT® HCV RNA 3.0 Assay (bDNA)</td>
<td>615–7,700,000 IU/mL</td>
<td>&lt;0.1 log_{10}</td>
<td>98.8% at detection cutoff</td>
<td>16.4%–32.4% CV</td>
<td>Non-1 genotypes quantified within 1.5-fold of genotype 1</td>
</tr>
<tr>
<td>Roche AMPLICOR MONITOR (PCR)</td>
<td>600–500,000 IU/mL</td>
<td>&lt;0.3 log_{10}</td>
<td>100% at detection cutoff</td>
<td>~18%–39% CV</td>
<td>Measured values from various genotypes could differ from expected values</td>
</tr>
</tbody>
</table>

HCV RNA Tests:
Differences and Dilemmas
Robert G. Gish, MD

Notes to Myself for Questions at the Meeting:

Slide 3

Slide 4

From Diagnosis to Treatment: The Full Spectrum of Care in Hepatitis C
### HCV RNA Tests: Differences and Dilemmas

Robert G. Gish, MD

Notes to Myself for Questions at the Meeting:

### In-House Validated Reference Lab HCV Quantitative Assay Characteristics

<table>
<thead>
<tr>
<th>Quest Heptimax</th>
<th>NGI SuperQuant¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dynamic range</td>
<td>TMA Quant: 5–7,500 IU/mL,¹ Real-time PCR: 50–7,000,000 IU/mL,¹</td>
</tr>
<tr>
<td>Linearity</td>
<td>N/A²</td>
</tr>
<tr>
<td>Specificity</td>
<td>N/A²</td>
</tr>
<tr>
<td>Precision</td>
<td>N/A²</td>
</tr>
<tr>
<td>Genotype quantification</td>
<td>N/A²</td>
</tr>
</tbody>
</table>

¹ Quest Diagnostics, data on file. ² No peer-reviewed data available. ³ Laboratory Corporation of America, data on file.

### Early Virologic Response

#### Percent Stopping Therapy for Lack of EVR

<table>
<thead>
<tr>
<th>EVR Definition</th>
<th>EVR Timepoint</th>
<th>Percent Stopped</th>
<th>SVR Missed</th>
<th>Estimated Cost Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV RNA (-)</td>
<td>4 wk</td>
<td>72%</td>
<td>56%</td>
<td>59%</td>
</tr>
<tr>
<td>HCV RNA (-) or ≥2-log drop</td>
<td>4 wk</td>
<td>35%</td>
<td>11%</td>
<td>29%</td>
</tr>
<tr>
<td>HCV RNA (-) or ≥1-log drop</td>
<td>4 wk</td>
<td>20%</td>
<td>3%</td>
<td>17%</td>
</tr>
<tr>
<td>HCV RNA (-)</td>
<td>12 wk</td>
<td>38%</td>
<td>10%</td>
<td>31%</td>
</tr>
<tr>
<td>HCV RNA (-) or ≥2-log drop</td>
<td>12 wk</td>
<td>19%</td>
<td>0.6%</td>
<td>16%</td>
</tr>
<tr>
<td>HCV RNA (-) or ≥1-log drop</td>
<td>12 wk</td>
<td>12%</td>
<td>0.6%</td>
<td>10%</td>
</tr>
<tr>
<td>HCV RNA (-)</td>
<td>24 wk</td>
<td>28%</td>
<td>3%</td>
<td>23%</td>
</tr>
</tbody>
</table>

Early Virologic Response

Conclusions

- Viral load and reductions in viral load can be used early in treatment to predict nonresponse to PEG IFN/RBV
- If HCV RNA fails to become negative or fall by at least 2 logs at week 12 of PEG IFN RBV
  - Therapy will not be successful and can be stopped
- Patients with detectable HCV RNA at week 12 despite a ≥2-log drop should be retested at 24 weeks
  - Stop treatment if HCV is still present

HCV RNA Tests:
Differences and Dilemmas

Robert G. Gish, MD

Notes to Myself for Questions at the Meeting:
### In-House Validated Reference Lab

**HCV Qualitative Assay Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Quest</th>
<th>NGI SuperQual Diagnostic Assay*1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assay sensitivity</td>
<td>No qualitative assay promoted</td>
<td>7.6 IU/mL¹</td>
</tr>
<tr>
<td>Assay specificity</td>
<td>No qualitative assay promoted</td>
<td>&gt;99%¹</td>
</tr>
<tr>
<td>Genotype recognition</td>
<td>No qualitative assay promoted</td>
<td>Equivalent detection of HCV genotypes¹</td>
</tr>
</tbody>
</table>

*NGI UltraQual assay approved for blood screening only.

¹ Laboratory Corporation of America, data on file.

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**Detection of HCV RNA by TMA But Not By PCR at EOT in Relapsing Patients**

**PEG-IFN**

<table>
<thead>
<tr>
<th>Response*</th>
<th>N</th>
<th>EOT</th>
<th>EFU</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG-IFN treated patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sustained responder</td>
<td>78</td>
<td>3 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>ETR responder/relapse</td>
<td>60</td>
<td>4 (7%)</td>
<td>60</td>
</tr>
<tr>
<td>Nonresponder</td>
<td>39</td>
<td>39 (100%)</td>
<td>39</td>
</tr>
<tr>
<td>Standard-IFN treated patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ETR responder/relapse</td>
<td>18</td>
<td>6 (33%)</td>
<td>18</td>
</tr>
</tbody>
</table>

* Based on RT-PCR results (COBAS Amplicor HCV 2.0)

HCV RNA Tests: Differences and Dilemmas
Robert G. Gish, MD

Notes to Myself for Questions at the Meeting:

Summary

- HCV genotyping is the standard of care.
- The best test for monitoring response during anti-HCV treatment is the assay with the widest dynamic range.
- A description of viral status includes three parameters.
  - Detection of virus
  - Quantification of virus
  - Characterization of viral sequences
- When HCV RNA level is denoted by a “>X” value, retest using an assay with a wider range (ie, bDNA assay).
- To support viral clearance, use the test with the lowest HCV RNA sensitivity.

Slide 12
Numerous grading systems have been used in an attempt to semiquantify the degree of fibrosis and inflammation in patients with chronic hepatitis C. The major use of these systems is to determine the need for treatment and the potential risk of disease progression. In addition, successful antiviral therapy with viral eradication is associated with both short- and long-term histologic improvement in inflammation and reversal of fibrosis in some patients with advanced disease. The ability to monitor these improvements, as well as progression in patients who have not responded or remain untreated, still relies heavily on liver biopsy. 

Liver biopsy examines the static mass of fibrosis in patients with hepatitis C, but may not reflect treatment- or immune-mediated changes in extracellular matrix remodeling. As such, biopsy is not an accurate marker of this dynamic process of constant degradation, formation, and remodeling. Recently, a study of 124 hepatitis C patients with laparoscopic biopsies of both right and left lobes indicated a discordance of at least one stage of fibrosis in 33% of patients. Other studies verify these results, and indicate a concordance rate of only 50% to 85% depending on the population of patients included. Thus, liver biopsy, the current gold standard for assessment of fibrosis and inflammation, may be less than ideal. An optimal test to determine the degree of fibrosis in patients with hepatitis C would detect dynamic changes, be specific for liver disease, detect small changes widely applicable to multiple liver diseases, be reproducible, and be cost-effective.

Liver biopsy has a number of other limitations as well. In addition to problems associated with variability in sampling error, there is variability between pathologists in their readings of histologic samples. A liver biopsy is also invasive and is associated with a small but finite risk of hemorrhage and postprocedure pain. These potential complications, coupled with the cost of the procedure, make the test difficult for some patients to accept. As such, while liver biopsy is frequently recommended, it is not mandatory and not necessarily
required in all patients prior to consideration of antiviral therapy for hepatitis C infection.

A number of algorithmic-based serum assays have evaluated markers with high prognostic values for significant fibrosis. While the details of these various assays and their algorithmic approaches vary, their degree of sensitivity and specificity, and their negative and positive predictive values indicate that their performance characteristics are similar to those described for liver biopsy. The exact role of these assays and how they perform longitudinally in following patients over many years of disease progression and regression have yet to be evaluated. One such panel of markers developed and validated in over 600 patients with hepatitis C can differentiate patients with mild or no fibrosis from those patients with more severe grades of fibrosis. The main utility of these assays may be in ruling out significant fibrosis without employing liver biopsy.

Patients without significant fibrosis may elect observation rather than treatment, or in the case of genotype 2/3 infection, may undergo treatment without a biopsy. Further prospective studies to validate these assays in hepatitis C patients in an external collaborative setting are now required. Currently, these assays should be considered when liver biopsies are contraindicated, when there is a need to monitor patients over time, and in situations in which liver biopsies are inadequate for interpretation.

**Suggested Readings**


Monitoring of Disease Progression: Assessment of Fibrosis Using Liver Biopsy and Noninvasive Markers

John G. McHutchison, MD

Notes to Myself for Questions at the Meeting:

Need for Alternative Fibrosis Markers

- Biopsy determines static mass of fibrosis
- Indirect marker of liver injury
- May not be reflective of a drug-induced change in ECM remodelling
- Ideal test
- Detect dynamic changes
  - Specific for liver disease
  - Able to detect small changes widely applicable to multiple liver diseases
  - Reproducible
Monitoring of Disease Progression: Assessment of Fibrosis Using Liver Biopsy and Noninvasive Markers

John G. McHutchison, MD

Notes to Myself for Questions at the Meeting:

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Panel of Fibrosis Markers

**Rationale**

- Combination of markers may have better predictive values for detecting the presence of significant fibrosis (eg, METAVIR F2–F4)
- Goals
  - High degree of accuracy
  - Reproducibility
  - Easily measured
  - Relatively inexpensive

---

In Situ
Liver Injury
Scar Matrix-Activated Stellate Cells

In Serum: 5-Marker Panel
- Alpha2Macroglobulin
- Total Bilirubin
- Gamma GT
- Apolipoprotein A1
- Haptoglobin

Monitoring of Disease Progression: Assessment of Fibrosis Using Liver Biopsy and Noninvasive Markers

John G. McHutchison, MD

Notes to Myself for Questions at the Meeting:

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**Diagnosis of F2F3F4**

**5-Marker Panel vs Age, Platelet, Prothrombin**

- Sensitivity
- Specificity
- Accuracy
- NPV
- PPV

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**Panels of Fibrosis Markers**

**Summary of Available Data**

<table>
<thead>
<tr>
<th>Markers</th>
<th>Imbert Bismuth</th>
<th>Forns</th>
<th>Wai (APRI)</th>
<th>Patel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 339</td>
<td>N = 125</td>
<td>N = 192</td>
<td>N = 696</td>
</tr>
<tr>
<td>Prevalence</td>
<td>41%</td>
<td>26%</td>
<td>47%</td>
<td>52%</td>
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<tr>
<td>Sensitivity</td>
<td>77%</td>
<td>83%</td>
<td>82%</td>
<td>61%</td>
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<tr>
<td>Specificity</td>
<td>95%</td>
<td>90%</td>
<td>90%</td>
<td>96%</td>
</tr>
<tr>
<td>PPV</td>
<td>90%</td>
<td>66%</td>
<td>88%</td>
<td>93%</td>
</tr>
<tr>
<td>NPV</td>
<td>89%</td>
<td>96%</td>
<td>85%</td>
<td>73%</td>
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<tr>
<td>Accuracy</td>
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<td>86%</td>
<td>80%</td>
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<tr>
<td>Indeterminate</td>
<td>50%</td>
<td>49%</td>
<td>50%</td>
<td>29%</td>
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</tbody>
</table>

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Monitoring of Disease Progression: Assessment of Fibrosis Using Liver Biopsy and Noninvasive Markers

John G. McHutchison, MD

Notes to Myself for Questions at the Meeting:

- Liver biopsy
  - Variability in interpretation
  - Small finite risks and costs
  - ? gold standard
- Noninvasive fibrosis marker panels
  - Greatly improved in last 5 years
  - Role in practice needs refinement
  - Ability to separate stages need to be improved
  - Further studies necessary and under way

Summary

Slide 7

Slide 8
Over the past 5 years, significant advances have been achieved in the treatment of chronic hepatitis C virus (HCV) infection. The current standard of care is combination therapy with peginterferon alfa (PEG IFN) and ribavirin (RBV). The results of recent clinical trials indicate that sustained viral response may be achieved in approximately 54% to 56% of patients treated with PEG IFN/RBV for 48 weeks. More importantly, long-term studies suggest that these sustained viral responses are durable, consistent with HCV eradication, and may lead to regression of HCV-related liver disease among successfully treated patients.

To achieve such successful outcomes, adherence to HCV treatment is critically important. However, adherence to PEG IFN/RBV may be undermined by treatment-related side effects that prompt physicians to reduce treatment doses or discontinue therapy, and by poor treatment tolerability leading to patient dropout.

In large clinical trials, hemoglobin level declined in approximately two thirds of patients treated with PEG IFN/RBV, and hemolytic anemia occurred in 10% to 13% of patients treated with PEG IFN/RBV regimens, usually within the first few weeks of treatment. However, the problem may be more widespread in community-based patients. A recent retrospective multicenter survey of “real world” patients scheduled to receive IFN/RBV for chronic hepatitis C found that about one quarter failed to complete therapy. This study also identified anemia as the cause of 36% of treatment discontinuations. Moreover, in a recent retrospective review of 770 charts from HCV-infected patients in 209 centers, about half (58% of men and 46% of women) had a ≥3 g/dL reduction in hemoglobin. RBV dose reduction was four times more likely if hemoglobin dropped to ≤12 g/dL and nearly 2.5 times more likely if a ≥3 g/dL reduction in hemoglobin occurred compared with those who had hemoglobin >12 g/dL or experienced a <3 g/dL reduction, respectively.

Similarly, PEG IFN-related neutropenia occurs in as many as 20% of patients, requiring dose reduction of
PEG IFN. In addition, fatigue (which may be exacerbated by anemia) and other neuropsychiatric effects of treatment occur in nearly 80% of patients and commonly result in patient-driven treatment discontinuation.

Dose reductions have been associated with decreased antiviral efficacy, and generally produce only small increases in blood cell counts when performed for hematologic toxicity. Accordingly, to maximize treatment outcomes of PEG IFN/RBV therapy, strategies are needed to reduce the medical necessity for dose reduction or treatment discontinuation and to improve patient quality of life to limit early withdrawal from therapy. Research is underway to evaluate the safety and effectiveness of cell-stimulating factors, such as filgrastim, darbepoetin, and epoetin alfa, to correct treatment-associated neutropenia and anemia, respectively. To date, randomized, placebo-controlled clinical trials have demonstrated that adjuvant epoetin alfa can effectively prevent RBV dose reduction, increase hemoglobin, and improve patient quality of life in anemic patients treated with PEG IFN/RBV. Similarly, antidepressants, such as selective serotonin reuptake inhibitors and other agents, are increasingly used to improve mood disorders in patients treated with IFN-based therapy.

To optimize outcomes with current therapies for HCV infection, aggressive recognition and management of treatment adverse effects are essential to increase medication delivery and tolerability.

**Suggested Readings**


Optimizing Outcomes in Patients Treated with Peginterferon/Ribavirin

Mark S. Sulkowski, MD

Notes to Myself for Questions at the Meeting:

Slide 1

Slide 2
Common Treatment-Limiting Factors

- Fatigue
- Neuropsychiatric effects
  - Depression, insomnia, irritability
- Hematologic effects
  - Anemia
  - Neutropenia
  - Thrombocytopenia
- Miscellaneous nuisances
  - Rash, cough, dyspepsia, weight loss
Consequences of Anemia

- Mean Hb ↓ 2.9–3.1 g/dL
- RBV: hemolytic anemia
- IFN: bone marrow suppression

↓ Adherence
↓ RBV Dose ↓ or Discontinued
↑ Side Effects
↓ SVR


Optimizing Outcomes in Patients Treated with Peginterferon/Ribavirin

Mark S. Sulkowski, MD

Notes to Myself for Questions at the Meeting:

Lowest Hb During Therapy by Gender

Optimizing Outcomes in Patients Treated with Peginterferon/Ribavirin

Mark S. Sulkowski, MD

Notes to Myself for Questions at the Meeting:

Slide 7

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Slide 8

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From Diagnosis to Treatment: The Full Spectrum of Care in Hepatitis C
Epoetin alfa Maintains RBV Dose

Study Entry

Week

Mean Ribavirin Dose (mg/d)


*P < .05

Optimizing Outcomes in Patients Treated with Peginterferon/Ribavirin

Mark S. Sulkowski, MD

Notes to Myself for Questions at the Meeting:

Neutropenia Complicates Therapy

PEG IFN α2b PEG IFN α2a

Stop <1% <1%

Dose reduction 18% 20%

Serious infection 2% 4%

No temporal relationship between ANC and infection

Correction of Neutropenia

- G-CSF 300 µg SC ~2–3 per wk
  - For patients with ANC <500/mm³ in the first 12 wk of therapy
- Outcomes
  - Prevent dose reduction: Yes
  - Increase SVR: Unknown
  - Decrease infection: Unknown
  - Make the doctor happier: Yes

Management of Neuropsychiatric Effects of Anti-HCV Therapy

- Anemia
- Thyroid (hyper or hypo)
- New medical conditions
- Other psychosocial stressors

Mild
- Reassure and counsel
- Increase clinical monitoring
- Adjuvant medications

Moderate
- Reassure and counsel
- Consider dose reduction
- Adjuvant medications
- Increase clinical monitoring
- Psychiatric referral

Severe
- Discontinue IFN
- Psychiatric referral

Armed with the latest information on hepatitis C diagnostic and monitoring tools, and new strategies on managing side effects, today’s clinician can develop more refined treatment plans to maximize outcomes for each hepatitis C patient. The cases presented in this discussion illustrate the clinical applications of these new tools and management strategies. Specific cases will provide attendees with a practical perspective on translating the information presented earlier into the clinical care of hepatitis C patients today.
Maximizing Today’s Therapeutic Tools to Meet the Challenges of Hepatitis C

Ira M. Jacobson, MD

Notes to Myself for Questions at the Meeting:

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Management of hepatitis C has become sophisticated. New technologies and treatment strategies provide many opportunities for successful treatment outcomes for the majority of patients.

Once a diagnosis has been confirmed, management begins with baseline evaluation not only of clinical status, but virologic factors such as viral level and genotype, and histologic features. These measurements help determine the best treatment strategy for the individual patient. Accurate and sensitive determinations of HCV RNA and genotype can be made using the latest technologies. It is important to utilize assays with a wide dynamic range of detection and excellent sensitivity/specificity.

Liver biopsy, the current standard of care for histologic assessment, has a number of limitations: It is invasive, measures the static mass of fibrosis, and is subject to variation in interpretation. It is not reflective of the dynamic process of degradation, formation, and remodeling that takes place in the liver as a result of disease processes and treatment-induced changes. New, less-invasive serum markers are being studied and appear effective in measuring changes over time and identifying patients who do not have significant fibrosis. These tests require further validation, and their exact role has not yet been determined, but they may be considered when liver biopsy is contraindicated, when patients require monitoring over time, or when biopsy is inadequate for interpretation.

Peginterferon/ribavirin is the current standard of care, particularly for patients with genotype 1 infection, based on its efficacy and the convenience of once-weekly (rather than thrice-weekly) interferon injections. Viral levels should be quantified again at week 12, with undetectable HCV RNA or a 2-log decrease representing early virologic response (EVR) and predicting long-term response. This can be confirmed at the end of treatment and 6 months posttreatment with further HCV RNA assessment. Treatment duration is thus initially based on week-12 response and on genotype. Genotype 1 patients with an EVR should
continue treatment for 48 weeks. Shorter treatment (24 weeks) and possibly lower doses may be sufficient for patients infected with genotype 2 or 3. Some physicians also believe that it is unnecessary to measure EVR in this population given the high rates of response.

Adherence is now recognized as a critical component of management. Side effects are nearly universal and, if not managed aggressively, often lead to dose reductions or treatment discontinuation. Reductions in drug doses have been found to reduce the likelihood of sustained response to treatment. As a result, physicians are increasingly turning to adjunctive therapies to manage side effects, and have come to recognize the importance of patient education and motivation in maintaining treatment regimens. For example, erythropoietin-stimulating proteins, antidepressants, and over-the-counter therapies are just some of the commonly used treatments to manage anemia, depression, and headache/flulike symptoms, respectively. EVR can be another important tool for motivating patients. Patients should be made to understand the necessity of treatment adherence particularly during the first 12 weeks, with EVR as an important treatment goal.

Once EVR is achieved, the likelihood of sustained response with continued treatment can serve to further motivate patients to stay on therapy.

Thus, new technologies for assessing and monitoring disease, and new approaches to optimize available treatments, provide an excellent chance for successful treatment of hepatitis C in today’s patients.
From Diagnosis to Treatment:
The Full Spectrum of Care in Hepatitis C

A CME Satellite Symposium presented during the 54th AASLD Annual Meeting
This program is not affiliated with AASLD

Syllabus
Monday, October 27, 2003
Boston, Massachusetts