Hepatitis C: Diagnosis and Natural History

Tushar Patel, MBChB

Prevalence

<table>
<thead>
<tr>
<th></th>
<th>Worldwide</th>
<th>United States</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>170 million (3%)</td>
<td>3.9 million (1.8%)</td>
</tr>
<tr>
<td>Anti-HCV positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV RNA positive</td>
<td></td>
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</tr>
</tbody>
</table>

Risk Factors

- Injection Drug Use
- Blood Transfusion or Organ Transplant Prior to 1992
- Birth from Infected Mother
- Mass Injections and Traditional Practices
- Multiple Sexual Partners
- Long-Term Hemodialysis
- Clotting Factor Treatment Prior to 1987

### Current Likelihood of Transmission

- **Transfusion**: ~1 in 1,000,000
- **Heterosexual partner**: ~1 in 1,000 per yr
- **Needlestick injury**
  - HCV-positive source: ~5%
  - HCV status unknown: ~1%
- **Maternal-Infant**
  - Mother HIV-negative: ~5%
  - Mother HIV-positive: 15-20%

### Diagnostic Tests

- Hepatitis C antibody tests
- Qualitative HCV RNA tests
- Quantitative HCV RNA tests
- Genotyping
- Liver biopsy

### Diagnosis and Evaluation

### Acute Hepatitis C Infection

- ALT (IU/L)
- Normal ALT
- HCV RNA positive
- Anti-HCV
- Symptoms

![Graph showing ALT levels over time with peaks indicative of acute hepatitis C infection](Hoofnagle JH, Hepatology 1997; 26:155)
**Antibody tests for hepatitis C**
- Indicates past or present infection
- Inexpensive, sensitive and specific
- Poor positive predictive value in low prevalence populations
- Low sensitivity in immunosuppressed patients

**HCV Genotypes**
- Six major genotypes found throughout the world
- Major determinant of response to antiviral therapy
- In Europe and U.S., 60-70% of patients have genotype 1 infection

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**Qualitative tests for HCV RNA**
- Confirms diagnosis of HCV infection
- Useful in the early diagnosis of acute hepatitis C
- Demonstrates the presence of active infection
- “Gold standard” for documenting response to treatment

**Virological Tests Do Not Predict Natural History of Disease**
- No correlation between genotype and progression of disease
- No correlation between HCV RNA level and progression of disease
Liver Biopsy

- Degree of fibrosis is most important predictor of prognosis
- Useful in determining need for anti-viral therapy
- Advanced cirrhosis associated with reduced response to treatment

Natural History

Stages of Fibrosis In Chronic Hepatitis

Outcome Following Hepatitis C Infection

<table>
<thead>
<tr>
<th>Time (yr)</th>
</tr>
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<tbody>
<tr>
<td>10</td>
</tr>
<tr>
<td>20</td>
</tr>
<tr>
<td>30</td>
</tr>
</tbody>
</table>

- Acute hepatitis C: 55 - 85%
- Chronic infection: 70%
- Chronic hepatitis: 20%
- Cirrhosis: 1 - 4%/yr
- Decompensation: 4 - 5%/yr
- HCC
Stage of Disease Correlates With Duration of Infection

Chronic hepatitis
Liver cirrhosis
Hepatocellular carcinoma

Years since transfusion

Median


Hepatocellular Carcinoma Incidence in HCV-Positive Cirrhosis

Outlook for Those With Compensated Cirrhosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Number</th>
<th>Follow-up (yr)</th>
<th>Decompensation (%/yr)</th>
<th>HCC (%/yr)</th>
<th>5-Year Survival (%)</th>
<th>Post decompensation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>384</td>
<td>5.0</td>
<td>3.9</td>
<td>1.4</td>
<td>91</td>
<td>50</td>
</tr>
<tr>
<td>B</td>
<td>112</td>
<td>4.5</td>
<td>4.4</td>
<td>2.3</td>
<td>83</td>
<td>51</td>
</tr>
<tr>
<td>C</td>
<td>103</td>
<td>3.3</td>
<td>5.0</td>
<td>3.3</td>
<td>84</td>
<td>--</td>
</tr>
</tbody>
</table>

Factors Associated With Fibrosis

- Duration of infection
- Alcohol > 50 gm per day
- Age > 40 years at infection
- Male gender

Poynard T, et al., Lancet 1997; 349:825

A: Fattovich G et al. Gastroenterology 1997;112:463
B: Hu K & Tong MJ. Hepatology 1999;29:1311
Progression to Cirrhosis Can Be Estimated From Initial Stage of Liver Biopsy Fibrosis

Fibrosis Rate Varies Among HCV-Infected Individuals

Fibrosis Risk Varies Among Individuals

<table>
<thead>
<tr>
<th></th>
<th>Patient A</th>
<th>Patient B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at infection</td>
<td>25</td>
<td>42</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>Seldom</td>
<td>3-4 drinks/day</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Fibrosis stage/yr</td>
<td>0.10</td>
<td>0.25</td>
</tr>
<tr>
<td>Years to cirrhosis</td>
<td>40</td>
<td>16</td>
</tr>
</tbody>
</table>

HIV Co-Infection May Accelerate Progression to Cirrhosis

Adapted from Di Martino V et al. Hepatology 2001;34:1193
Should we treat Hepatitis C?

- HCV is the only chronic virus infection that can be eradicated (cured) by antiviral therapy.
- Cure of infection (SVR) essentially eliminates risk of decompensation in patients with cirrhosis and dramatically reduces risk of HCC.

Liver-Related Mortality in Chronic Infection

<table>
<thead>
<tr>
<th>Duration of Follow-Up</th>
<th>Middle-Aged Transfusion Recipients</th>
<th>Young Air Force Recruits</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 Years</td>
<td>% Mortality From Liver Disease 2</td>
<td></td>
</tr>
<tr>
<td>n=377</td>
<td>4%</td>
<td>n=222</td>
</tr>
<tr>
<td>n=851</td>
<td></td>
<td>n=17</td>
</tr>
</tbody>
</table>

Future Prevalence of HCV

Results of a Markov Model Based on HCV Natural History Studies*

<table>
<thead>
<tr>
<th>Year</th>
<th>Estimated % Increase From 2000 to 2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>0%</td>
</tr>
<tr>
<td>2010</td>
<td>81%</td>
</tr>
<tr>
<td>2020</td>
<td>181%</td>
</tr>
</tbody>
</table>

HCV Related Complications Expected to Increase Greatly in the Coming Years

- HCC 81%
- Cirrhosis 82%
- Decompensation 106%
- Liver-Related Deaths 181%
Pre-treatment evaluation

Current Practice

<table>
<thead>
<tr>
<th>HCV viral load</th>
<th>Hepatitis A/ B immunizations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-HAV</td>
<td>AFP</td>
</tr>
<tr>
<td>HBsAg</td>
<td>+/- US, EGD</td>
</tr>
<tr>
<td>TBI</td>
<td>Liver Biopsy</td>
</tr>
<tr>
<td>ALT</td>
<td></td>
</tr>
<tr>
<td>CBC</td>
<td></td>
</tr>
</tbody>
</table>

Patient referral
- Natural history of HCV
- Treatment options
- Adverse effects of Rx
- Expected benefits of Rx
- Duration of treatment

Mental Health Evaluation
- Psychopathology (e.g., substance abuse, depression, anxiety) is prominent in individuals with chronic HCV
- Pegylated IFN, with or without ribavirin, is associated with depression rates of 20%-34%
- IFN-α and ribavirin can worsen and/or induce depression and other underlying psychiatric conditions
- Patients should be screened and have any pre-existing psychiatric conditions treated before initiating HCV treatment

Predictors of Response to Antiviral Therapy in Chronic Hepatitis C
- Genotype 1 and 4 are less responsive than other genotypes
- High viral load is less responsive
- Advanced fibrosis is less responsive
Hepatitis C
Current and Future Treatment
Maher Azzouz, MD
Associate Professor of Medicine
Director of Endoscopy
Division of Gastroenterology Hepatology and Nutrition
The Comprehensive Transplant Center
The Ohio State University

Goals of HCV Therapy

- Primary goal: eradicate the virus
- Secondary goals
  - Slow disease progression
  - Minimize risk of HCC
  - Improve liver histology
  - Enhance quality of life
  - Prevent transmission of virus
  - Reduce extrahepatic manifestations

Virologic Responses

- PegIFN/RBV
- SVR
- RVR
- cEVR
- EVR
- Slow virologic response
- Limit of detection

Suboptimal Virologic Responses

- Null response
- Relapse
- Breakthrough
- Partial response
- 2 log₁₀ decline
- Limit of detection
HCV Therapy
SVR/Standard Interferon (IFN)


HCV Therapy
SVR With PegIFN/Ribavirin

• > 50% of GT 1 Patients Do Not Respond

  - PegIFN alfa-2b 1.5 µg/kg/week + RBV 800 mg/day for 48 weeks\(^1\)
  - PegIFN alfa-2a 180 µg/week + weight-based RBV (1000 or 1200 mg/day) for 48 weeks\(^2\)


IDEAL Trial
Which PegIFN is better

Genotype 1 US Patients

There were no statistical differences between groups

Peg-IFN + RBV
Response Rates


HCV Treatment Challenges

- Difficult-to-Treat HCV Patient
- Preventing Relapse
- Retreatment Options for Treatment Failure
- Maintenance Therapy
- Future Options for Treatment

Duration of Undetectability

- Longer Duration of Undetectability on Treatment Increases Chance for SVR

Ribavirin Dosage/Adherence

- Higher Ribavirin dose and cumulative dose are associated with increased SVR
Steatosis in HCV

- Steatosis is a common comorbidity of HCV
- Found in 50% to 60% of HCV-infected patients vs 14% to 30% in general population

Proportion of Patients With Fatty Liver Disease Among 121 HCV-Infected Individuals With Available Liver Biopsies

<table>
<thead>
<tr>
<th>No steatosis (41%)</th>
<th>Steatosis (41%)</th>
<th>NASH (18%)</th>
</tr>
</thead>
</table>

2 Types of Steatosis in Hepatitis C

- Metabolic syndrome
- Insulin resistance
- Overweight
- Diabetes
- Alcohol

HCV
- Viral steatosis (viremia)
- GT 3

Viral steatosis may disappear following successful hepatitis C therapy

Effect of Weight Loss on Antiviral Response

- Role of insulin sensitizers
- 32 treatment-naive GT 1 HCV patients with metabolic syndrome
- 15 patients on low-calorie diet: 10% ↓ in BMI
- HOMA: 4.86-3.45 (P = .0018)
- pegIFN alfa-2b + RBV
- Response: 60.0%
- 17 control patients
- Response: 17.6%

HCV Treatment: Key Predictors of Response

<table>
<thead>
<tr>
<th>1995-2000</th>
<th>Current</th>
</tr>
</thead>
<tbody>
<tr>
<td>• GT 2 or 3</td>
<td>• Lack of steatosis</td>
</tr>
<tr>
<td>• Absence of fibrosis</td>
<td>• Adherence</td>
</tr>
<tr>
<td>• Low HCV RNA</td>
<td>• Early response</td>
</tr>
<tr>
<td>• Younger age</td>
<td>• RBV dosage</td>
</tr>
<tr>
<td>• Female sex</td>
<td>• Race</td>
</tr>
<tr>
<td>• Weight</td>
<td>• Co-infection</td>
</tr>
</tbody>
</table>

References:
HCV Patient Projections

HCV Retreatment

Outcome in Nonresponders to IFN-Based Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>GT</th>
<th>N (Previous Treatment)</th>
<th>SVR Rate (Previous Treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jacobson[1]</td>
<td>PegIFN alfa-2b + RBV x 48 weeks</td>
<td>1</td>
<td>47 (IFN) 219 (IFN/RBV)</td>
<td>21% (IFN) 8% (IFN/RBV)</td>
</tr>
<tr>
<td>Sherman[2]</td>
<td>PegIFN alfa-2a + RBV x 48 weeks</td>
<td>1</td>
<td>36 (IFN) 148 (IFN/RBV)</td>
<td>22% (IFN) 20% (IFN/RBV)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2/3</td>
<td>9 (IFN) 19 (IFN/RBV)</td>
<td>44% (IFN) 37% (IFN/RBV)</td>
</tr>
<tr>
<td>RENEW[3]</td>
<td>PegIFN alfa-2b 1.5 or 3.0 µg/kg/week + RBV</td>
<td>1 (91%)</td>
<td>704 (IFN/RBV)</td>
<td>12% (IFN) 17% (IFN/RBV)</td>
</tr>
<tr>
<td>HALT-C[4]</td>
<td>PegIFN alfa-2a + RBV x 48 weeks</td>
<td>All</td>
<td>604</td>
<td>18%</td>
</tr>
<tr>
<td>EPIC[5]</td>
<td>PegIFN alfa-2b + RBV x 48 weeks</td>
<td>1 (81%) 2/3 (19%)</td>
<td>903</td>
<td>18%</td>
</tr>
</tbody>
</table>


Outcome in Nonresponders to PegIFN/RBV

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>GT</th>
<th>N (Previous Treatment)</th>
<th>SVR Rate (Previous Treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>REPEAT[1]</td>
<td>PegIFN alfa-2a + RBV x 48 weeks</td>
<td>1 (&gt; 90%)</td>
<td>473</td>
<td>8%</td>
</tr>
<tr>
<td></td>
<td>PegIFN alfa-2a + RBV x 72 weeks</td>
<td>1 (&gt; 90%)</td>
<td>469</td>
<td>16%</td>
</tr>
<tr>
<td>EPIC[2]</td>
<td>PegIFN alfa-2b + RBV x 48 weeks</td>
<td>1 (81%) 2/3 (15%)</td>
<td>196 (PegIFN alfa-2a) 280 (PegIFN alfa-2b)</td>
<td>6% (PegIFN alfa-2a) 7% (PegIFN alfa-2b)</td>
</tr>
</tbody>
</table>

HCV Retreatment: DIRECT

Sustained Virologic Response in Nonresponders to PegIFN/Rib

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>GT</th>
<th>N</th>
<th>SVR Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIRECT</td>
<td>CIFN 9 µg/day + RBV</td>
<td>1 (95%)</td>
<td>245</td>
<td>6.9%</td>
</tr>
<tr>
<td></td>
<td>CIFN 15 µg/day + RBV</td>
<td>1 (96%)</td>
<td>242</td>
<td>10.7%</td>
</tr>
</tbody>
</table>


HCV Retreatment: Relapsers

Outcomes in Relapsers to PegIFN-Based Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>GT</th>
<th>N</th>
<th>SVR Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaiser</td>
<td>CIFN 9 µg/day + RBV x 72 weeks</td>
<td>1</td>
<td>120</td>
<td>69%</td>
</tr>
<tr>
<td></td>
<td>PegIFN alfa-2a + RBV x 72 weeks</td>
<td></td>
<td></td>
<td>42%</td>
</tr>
</tbody>
</table>


8-Year Posttreatment Outcomes: Patients With or Without SVR

Liver-Related Death

- SVR: 4.4% (CI: 0% to 12.9%)
- No SVR: 12.9% (CI: 7.7% to 18.6%)
- \( P < 0.001 \) (log likelihood)

Liver Failure

- SVR: 0% (CI: 0% to 0.2%)
- No SVR: 13.3% (CI: 8.4% to 18.2%)
- \( P = .001 \) (log likelihood)

Antiviral Therapy for HCV-Related Cirrhosis: Prevention of HCC

- Does it prevent HCC?
  - Early studies suggested reduced risk of HCC following IFN treatment, even if treatment was unsuccessful
  - Later studies indicate some benefit but only in noncirrhotic patients achieving SVR
  - Studies in HCV patients with cirrhosis do not show significant reduction in HCC after antiviral treatment
- Conclusion: If advanced fibrosis or cirrhosis is present, patients remain at risk for HCC, even after achieving SVR

Maintenance Therapy: COPILOT

Event-Free Survival With and Primary Endpoints (ITT)

49% of patients did not achieve 4-year event-free survival

- Primary endpoints more common in both colchicine and pegIFN arms in patients with portal HTN (32% and 23%, respectively) vs without portal HTN (9% and 13%, respectively)


Maintenance Therapy: HALT-C

Long-term PegIFN alfa-2a 90 µg/week in Nonresponders

- No reduction in fibrosis and no difference between arms
- No significant difference between arms in any primary outcome
  - 34.1% vs 33.8% (HR: 1.01; 95% CI: 0.81-1.26)

Outcomes at 3.5 Years

(P = NS for all comparisons)

- No treatment (n = 533)
- PegIFN alfa-2a 90 µg/week (n = 517)*

Patients (%)

Death
Decompensation
HCC
Increase in Fibrosis

*17% discontinued at 1.0 year and 30% discontinued at 3.5 years


Future Options for Treatment
Boceprevir + PegIFN/RBV: Phase II Nonresponder Study, GT 1

- Response dependent on IFN responsiveness

Patients With Detectable HCV RNA or $\geq 2\,\log_{10}$ Decline in HCV RNA at $\geq 12$ Weeks of Previous PegIFN + RBV (N = 357)

<table>
<thead>
<tr>
<th>PegIFN alfa-2b + RBV</th>
<th>Boceprevir$^*$ + PegIFN alfa-2b + RBV (Various Arms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRV (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td></td>
</tr>
<tr>
<td>80</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td></td>
</tr>
</tbody>
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*100, 200, 400, and 800 mg TID.


Telaprevir + PegIFN alfa-2a + RBV in Nonresponders or Relapsers

- Open-label treatment of patients from control arms of PROVE1-3 trials

<table>
<thead>
<tr>
<th>Week 4 Null Responder$^*$</th>
<th>Week 12 Null Responder$^*$</th>
<th>Partial Responder$^*$</th>
<th>Week 20 Breakthrough</th>
<th>Relapser</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>33</td>
<td>67</td>
<td>89</td>
<td>79</td>
<td>100</td>
</tr>
<tr>
<td>50</td>
<td>79</td>
<td>100</td>
<td>100</td>
<td>100</td>
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<tr>
<td>80</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^*$< 1 log$_{10}$ drop at Week 4. $^\dagger$< 2 log$_{10}$ drop at Week 12. $^\ddagger$≥ 2 log$_{10}$ drop at Week 12; detectable HCV RNA at Week 24.


AlbIFN Retreatment of IFN/RBV and PegIFN/RBV Nonresponders

<table>
<thead>
<tr>
<th>SVR, % (n/N)</th>
<th>AlbIFN alfa-2b + RBV$^*$ Every 4 Weeks</th>
<th>AlbIFN alfa-2b + RBV$^*$ Every 2 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1200 µg</td>
<td>900 µg</td>
</tr>
<tr>
<td>All patients</td>
<td>25 (6/24)</td>
<td>30 (7/23)</td>
</tr>
<tr>
<td>GT1, PegIFN/RBV nonresponders</td>
<td>15 (2/13)</td>
<td>15 (2/13)</td>
</tr>
</tbody>
</table>

- Overall SVR rate: 17.4%
- GT1, PegIFN + RBV nonresponder SVR rate: 10.7%

Discontinued Clinical Programs

<table>
<thead>
<tr>
<th>COMPANY</th>
<th>PRODUCT</th>
<th>PHASE</th>
<th>REASON FOR DISCONTINUATION</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roche/Inhibitex</td>
<td>Levovirin</td>
<td>Phase I</td>
<td>Lack of activity and formulation issues</td>
<td>L-isomer of RBV</td>
</tr>
<tr>
<td>Boehringer Ingelheim</td>
<td>BILN 2061</td>
<td>Phase II</td>
<td>Cardiac toxicity in animals</td>
<td>Protease inhibitor</td>
</tr>
<tr>
<td>Roche</td>
<td>R1626</td>
<td>Phase II</td>
<td>Safety</td>
<td>Polymerase inhibitor</td>
</tr>
<tr>
<td>Vertex Pharmaceuticals</td>
<td>Merimepodib (MMPD)</td>
<td>Phase II</td>
<td>Lack of efficacy</td>
<td>Polymerase inhibitor</td>
</tr>
<tr>
<td>Vertex Pharmaceuticals</td>
<td>Merimepodib (MMPD)</td>
<td>Phase II</td>
<td>Lack of efficacy</td>
<td>Immune response modifier</td>
</tr>
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<td>Phase II</td>
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<tr>
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<td>Phase II</td>
<td>Lack of efficacy</td>
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<td>Vertex Pharmaceuticals</td>
<td>Merimepodib (MMPD)</td>
<td>Phase II</td>
<td>Lack of efficacy</td>
<td>Immune response modifier</td>
</tr>
<tr>
<td>Achillion/Gilead</td>
<td>ACH806</td>
<td>Phase II</td>
<td>Safety</td>
<td>Protease Inhibitor</td>
</tr>
<tr>
<td>Idenix/Novartis</td>
<td>Valopicitabine NM283</td>
<td>Phase II</td>
<td>Clinical development on hold per FDA request for safety reasons</td>
<td>Polymerase Inhibitor</td>
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<td>Clinical development on hold per FDA request for safety reasons</td>
<td>Polymerase Inhibitor</td>
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</tbody>
</table>

HCV Therapy Conclusion

- Relapsers are good candidates for retreatment
- Nonresponders to suboptimal therapy (ie, standard IFN) more likely to respond to retreatment vs those previously treated with pegIFN/RBV
- Nonresponders with negative predictors of response (ie, advanced fibrosis, insulin resistance) may not be good candidates for retreatment

HCV Therapy Conclusion

Improving Outcome and Decreasing Relapse

- Importance of duration of HCV RNA negativity
- Slow responders may require longer duration of therapy (GT 1)
- Weight based dose of RBV
- Improving Compliance
  - Better management of adverse effects to decrease dose reductions or interruptions
- Steatosis and Insulin Resistance
- Some patients may be inherently resistant to IFN

HCV Therapy Conclusion

- Maintenance therapy has not been shown to be effective for reducing fibrosis progression, other disease outcomes
- Promising results with new compounds, even in the setting of null response
HCV therapy
Managing side effects

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Hepatitis C Therapy

- Pegylated interferon plus ribavirin
- Consensus interferon plus ribavirin
- Both regimens associated with possibly significant side effects.
- Front-load your patient education about side effects; it saves time later. Teach them what that might experience.

Multidisciplinary team
Identify / incorporate resources

- Psych: psychiatrist, psychologist, psych CNP.
- Substance abuse resources: Local / state AA information. AlAnon for friends, family. City / county resources, CD counselors.
- Opthamology: pre-treatment eye exams, especially in diabetic patients. Urgent referral is vision changes in patient on Rx.70
- Endocrinology: DM management.
- Cardiologist
- Pharmacist
- Weight management resources

Place side effects in perspective

- Patients get on the internet and read about other's bad experiences. People with bad experiences likely to be most outspoken.
- Present frequency of SEs as bell curve:
  ✓ Outliers left: no problems
  ✓ Outliers right: must DC treatment
  ✓ Largest number in the middle: flu-like sx around injection time, fatigue during week, but still working, functioning.
Fatigue - most common

- Hgb / thyroid – both are monitored
  → ? EPO / ? thyroid med may be indicated
- Interventions:
  ✓ Energy conservation measures. Be efficient.
  ✓ Assess for sleep time / sleep hygiene
  ✓ Plan A, B and C → patients love this.
  ✓ Regular moderate exercise. Walking 20 minutes daily.

Injection Site Reactions

- Determine if patient is using proper technique and proper site.
- Apply cool pack / ice pack to area.
- Use small amount of hydrocortisone 1% ointment to site between cold packs.
- Reinforce site rotation.

GI issues: N/V, anorexia, diarrhea

- Encourage small, frequent meals. Some pts develop changes in smell /taste.
- Intuitive eating. Oatmeal, peanut butter.
- “Boost” or “Ensure” blended with ice.
- Diarrhea – can take OTC antidiarrheal. Avoid fatty foods. Pt to contact office if vomiting and / or diarrhea becomes severe.

Insomnia

- Assess for sleep / nap patterns.
- Sleep hygiene: dark, quiet room. Regular bedtime.
- As with fatigue – regular, moderate exercise helpful.
- Benadryl 25 or 50mg PO HS PRN.
Pruritus
Rash, Dry skin, & Alopecia
Associated with both IFN and RIB

- Maintain adequate hydration, non-caffeinated beverages.
- Use warm, not hot water for bathing.
- Keep sleeping quarters cool enough to prevent perspiration.
- Lotions: Sarna or Eucerin Calming cream. Oatmeal based lotions (Aveeno).

Psychiatric Issues

- Patients should be screened for depression prior to initiation of therapy, and stabilized on an antidepressant if indicated. Consider psych follow-along in marginal patients.
- Journaling: encourage!
- Communication: encourage communication between patient, spouse, SO, friends and family.

Pruritus
Rash, Dry Skin, Alopecia

- Benadryl 25 mg tablets.
  - Drug is sedating. For daytime use, start at 12.5mg PO q 4-6h. Increase as tolerated.
  - 50 mg HS.
  - If rash is severe, check for autoimmune component.
  - Rash can be associated with both IFN and RIB.
  - Alopecia is reversible. Reassure patient.

Flu-like Symptoms
HA, Chills, Myalgias

- Interventions:
  - If not contraindicated, ibuprofen 400mg 30 minutes before IFN injection and continue q8h PRN the next 48 hours.
  - Tylenol, no more than 2,000mg daily. Educate re: acetaminophen in many OTCs. Read label.
  - Typically, these SEs improve over time.
### Cough

- Usually associated with ribavirin.
- Interventions:
  - OTC dextromethorphan.
  - Heating pad to chest (patient recommendation)
  - Rx Tessalon Perles 100mg. One or two perles TID PRN cough. (benzonatate).
  - CXR?

### Oral Problems

- Apthous ulcers, “sore mouth”. Try Magic mouthwash. =parts: Mylanta, Benadryl, lidocaine.
- Oral / oropharyngeal candidiasis. Rare, but can be very uncomfortable: anti-fungal rinse or systemic med.

### Red Flags

- Vision changes: Stop IFN - urgent opho referral
- Severe depression: SI, HI. Stop IFN!
- Severe rash with intractable pruritus.
- Monitor thyroid before, during, after therapy.
- Check autoimmune markers before starting.