Current and Future Treatment for Chronic Hepatitis C

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Greetings to you all from the High Country of Colorado!!!

Speaker Disclosure
I have financial relationships with commercial entities and the content of my presentation does include discussion of off-label/investigative use of interferon alfa-2b (INTRON A®), peginterferon alfa-2a (PEGASYS®) plus ribavirin (REBETOL®, COPEGUS®) and other potential therapies.

Research Grants, Speaker Bureau, Advisory Boards:
Roche, Schering, Intermune, Ortho Biotech, Idenix, Valeant, Tanox, XTL

Current Treatment

- The “Good”
- The “Bad”
- The “Ugly”

The “Good”

Success of Treatment

FDA-Approved Therapies
- Interferon Monotherapy
  - Interferon alfa-2b (Intron A)
  - Interferon alfa-2a (Roferon A)
  - Consensus interferon (Infergen)
  - Peginterferon alfa-2b (PegIntron)
  - Peginterferon alfa-2a (Pegasys)
- Interferon/Ribavirin Combination
  - Intron A + Rebetol (Rebetron)
  - Roferon A + Copegus
- Peginterferon/Ribavirin Combinations
  - PegIntron + Rebetol
  - Pegasys + Copegus
### Progress in Therapy

<table>
<thead>
<tr>
<th>Year</th>
<th>NonPegIFN</th>
<th>PegIFN</th>
<th>PegIFN-2a or -2b +R or daily ConIFN + R</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>1985</td>
<td>20%</td>
<td>40%</td>
<td>60%</td>
</tr>
<tr>
<td>1990</td>
<td>40%</td>
<td>60%</td>
<td>80%</td>
</tr>
<tr>
<td>1995</td>
<td>60%</td>
<td>80%</td>
<td>100%</td>
</tr>
<tr>
<td>2000</td>
<td>80%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>2005</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
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**SVR (%)**

**The “Bad”**

**Failure of Treatment**

### Limitations of Current Rx

- **Study populations may not reflect the general clinic population with HCV**
  - African Americans
  - Incarcerated, homeless
  - Substance abuse or psychiatric illness
  - Advanced disease
  - HIV coinfection
- **Side Effects limit dose, duration, and tolerance of treatment**
  - Flu-like symptoms
  - Neuro-psych changes
  - Cytopenias

### SVR is Less in Heavy Drinkers

- **Response in non-drinkers or light-drinkers**
  - 25% to 53% SVR
- **Response in heavy drinkers (>70 g/d)**
  - 0% to 16% SVR

### Demographics

- **Patients were naïve to prior therapy and had elevated ALT**
- **Total Number of Patients 106 (3:1 distribution, 78 AA, 28 Cau)**

<table>
<thead>
<tr>
<th>Demographics</th>
<th>AA</th>
<th>Cau</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Mean Age</td>
<td>46</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>- % Male</td>
<td>72%</td>
<td>81%</td>
<td></td>
</tr>
<tr>
<td>- HCV RNA &gt; 1 x 10^6 IU/ml</td>
<td>56%</td>
<td>43%</td>
<td></td>
</tr>
<tr>
<td>- &gt; 80% Adherence (Abst 322)</td>
<td>89%</td>
<td>89%</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>- % with Dose Decrease for WBC</td>
<td>37%</td>
<td>78%</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>SVR % (All patients)</td>
<td>36%</td>
<td>39%</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>SVR% (HVL)</td>
<td>18%</td>
<td>41%</td>
<td></td>
</tr>
</tbody>
</table>

*Abstract 307: Fibrosis improved in 25%, stable in 69% of AA
Fibrosis improved in 6%, stable in 88% of Cau*
SVR in IVDA in Treatment Programs

Impact of Severity of Cirrhosis

APRICOT Trial

HCV Virologic Responses
HCV Virologic Responses: Genotype 1

% HCV RNA negative

IFN+R PegIFN PegIFN+R

EOT

SVR

The “Ugly”

Harm of Treatment

Issues On the Job

“…… I was exhausted when I started taking interferon. My sister had died recently, and I thought it was depression that had me so tired. My doctor told me I had beginning cirrhosis, and I was so sick I needed to take time off from work.

I was incredulous. Taking time off was for operations! That was my own denial, my survival system. I was amazed my company did approve leave – and I was paranoid. I expected surveillance cameras to sneak up on me. When I finally went back to work, it was part time, then full time. It was rough. I was achey; I had headaches. I just stayed in my cubicle and did what I had to do.

I was afraid of losing my job. I didn’t know my rights. I thought if I had 6 absences in a row, I’d be out the door.”

Living with Hepatitis C, Everson & Weinberg, 2002

Issues On the Job

“…… I didn’t go to church for 6 months. I just slept. It’s a miracle I didn’t lose my business…..”

Living with Hepatitis C, Everson & Weinberg, 2002

Issues at Home

“…… When my husband started interferon, it changed our lives. We weren’t prepared for it. Interferon can be hard on the spouse, too. To be supportive, I had to plan things at a slower rate.…… During treatment, I would have to encourage him to take a half-hour walk on flat ground – just to get him off the couch and outside.”

Living with Hepatitis C, Everson & Weinberg, 2002

Personal Issues

“…….. I dropped 20 pounds because I had no appetite.”

“…….. It’s a peculiar kind of headache. I call it the interferon headache. Also, it seems as though I’m more forgetful. All my friends tell me they forget things, too, that I’m just getting older, but it seems different to me. Now I write everything – and I mean everything – down!”

“…….. My hairdresser told me my hair was thinning out …”

“…….. About midway through treatment, I had to go on an antidepressant ……”

“…….. My lower red blood count means I get less oxygen. …….. I feel faint, I slow down and take deep breaths ….”

Living with Hepatitis C, Everson & Weinberg, 2002
Sex, or rather Lack of

“...... I filled out this form that asked me if I felt good or bad. I don’t feel either. My sexual desire is gone. I feel like a machine......”

Living with Hepatitis C, Everson & Weinberg, 2002

Emotional Mutation

“...... It’s unbelievable to deal with your emotions. Every week they mutate, like the virus. Every week is different......”

Living with Hepatitis C, Everson & Weinberg, 2002

Serious Adverse Reactions (Rare)

• Suicide
• Infections
• Myocardial Infarction
• Thyroid disease
• Autoimmune disease
  – ITP
• Retinal hemorrhage

Future Treatment

• Variations on Current FDA-approved therapies
• New Interferons and Ribavirins
• New Innovative Molecular Approaches
• Therapeutic Vaccines

Retreatment of Rebetron NRs

Peginterferon alfa-2b + Ribavirin
  Jacobson 6% - 10%
  Teuber 6%
  Sulkowski 12%
  Lawitz 10%
  Selim 9%
  Gross 4% – 11%

Peginterferon alfa-2a + Ribavirin (HALT C)
  Shiffman, HALT C Lead-In 12%

Consensus IFN + Ribavirin
  Kaiser (induction) 39 – 44%

Retreatment of PegIFN+R NonResp

Peginterferon alfa-2b + Ribavirin
  ?

Peginterferon alfa-2a + Ribavirin
  REPEAT
  ?

Consensus IFN + Ribavirin
  Kaiser (induction) ~ 25%
**PegIFN Trials**

- **Slow Responders (Week 4, HCV RNA positive)**
  - PegIFN 2a + R: TERAVIC-4
  - PegIFN 2b + R: SUCCESS

- **African Americans**
  - PegIFN 2a + R: VIRAHEP-C
  - PegIFN 2b + R: WIN-R (Cohort)

- **Comparing Peg-to-Peg**
  - Schering: IDEAL
  - Roche: COMPARE
  - Roche: PEAK

**New Interferons and Ribavirins**

- **Human Genome Sciences**
  - Albuferon (Phase III)

- **Biolex/OctoPlus**
  - Locteran (ND)

- **Hemispherix/Esteve**
  - Ampligen (Phase IIb)

- **Roche**
  - Levovirin (withdrew)

- **Schering/Maxim**
  - Ceplone (withdrew)

- **Viramidine Trials**
  - ?EOT lower, SVR?

**Molecular Target HCV IRES**

- Target for Ribozyme
- Target for Antisense
- 5'

**Protein Targets for Specific HCV Antiviral Therapy**

- HCV Polyprotein
- NS 2/3 Metalloprotease
- Binds PKR

<table>
<thead>
<tr>
<th>NS3 Protease domain</th>
<th>NS3 Helicase domain</th>
<th>NS3/NS4 Bifunctional protease / helicase</th>
<th>NS5B RNA-dependent RNA polymerase</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS2</td>
<td>NS3</td>
<td>NS4A</td>
<td>NS5A</td>
</tr>
<tr>
<td>NS3</td>
<td>NS4A</td>
<td>NS4B</td>
<td>NS5A</td>
</tr>
</tbody>
</table>

**NS3 Protease Inhibitor**

- BILN 2061: Boehringer-Ingelheim
  - On Hold

**Protease Inhibitor**

- VX050: Vertex
  - Phase I

Potential Cardiotoxicity in Animal Models

Promising agent: just beginning clinical trials
RNA Polymerase Inhibitor

- NM283 (Idenix, NM283, Valopicitabine) Phase III
  - Monotherapy: 1.2 log drop at 12 weeks
  - with PegIFN: 3.2 log drop at 12 weeks, 75% EVR

Other Therapies

- Interferon beta
- ISIS
- SCH 6
- VX 950
- Amantadine
- Mycophenolate Mofetil
- Levovirin
- Merimepodib
- Viramidine
- Zadaxin
- Isatoribine
- Yirostat
- Action
- Ceplene
- HCV – 796

Clinical Trials: UCHSC 2005

- Human Genome Sciences
- Intermune
- United Therapeutics
- GSK
- NIH/Roche - HALT-C
- NIH/Schering – LADR
- Roche
- GlobelImmune
  - Albuferon (Phase III)
  - Alpha-Gamma Study
  - Relapse prevention
  - Thrombopoietin Stimulator
  - Maintenance Therapy
  - Pre-Transplant Therapy
  - Phoenix, post-Transplant
  - Therapeutic Vaccine

Conclusions

- Current therapy is effective in ~ 50%
  (45% geno 1, 80% geno non-1)
- New Approaches using approved therapies or
  New Therapies are needed
- Maintenance therapy will likely be needed for
  nonresponders with stage 3 – 4 fibrosis
- New treatments are emerging and the future
  of antiviral therapy against HCV looks promising.

Use of Herbal Supplements and CAM in the Treatment of Chronic Hepatitis C
Patients Visits to CAM Practitioners and Western MDs

JAMA 1998;280:1569-1575
Why do patients take CAM?

- Dissatisfaction with Western medicine
  - Inability to cure most disease/illness
  - Side Effects of and adverse reactions to treatments
  - Depersonalization
  - Patients feel they are viewed more as a disease than a person or individual

- Satisfaction with CAM
  - Providers have a more holistic approach
  - More one-on-one time in the patient-provider relationship
  - Concentration on “Wellness” and health maintenance, which encourages self-therapy and autonomy

Yoga

Unlocking the Liver by Massage

“Your liver alone travels 600 meters.”

Craniosacral Therapy
**Use of CAM in Hepatitis C**

- 40% to 60% of Hepatitis C patients use CAM
- Geographic variation, highest use (75%) in Southern CA
- Types Reported
  - Milk thistle 48%
  - Megavitamin therapy 8%
  - Thymus extract 4%
  - Ginseng 21%
  - St. John’s Wort 15%
  - Herbalists 16%
  - Naturopaths 15%
  - Chiropractors 4%


**Potentially Therapeutic Herbs**

- Glycyrrhizin (licorice root)
- Phyllanthus amarus
- Daphnoretin, costunilite (Clark’s root)
- Silymarin (Milk Thistle)
- Picroliv
- TJ-9 (extract of scutellaria, glycyrrhiza, bupleurum, ginseng)
- Compound 861 (aqueous extract of 10 Chinese herbs)
- LIV.52. (extract of several Ayurvedic herbs)


**Hepatotoxic Herbs & Mushrooms**

- Pyrrolizidine Alkaloids (teas, salads, herbs, capsules, dietary supplements)
  - Heliotropium, Senecio, Crotalaria
  - Symphytum (Comfrey)
- Atractylis gummifera & Callilepsis Laureola
- Teucrium Chamaedrys (Germander)
- Larrea Tridentata (Chaparral)
- Cassia Angustifolia (Senna)
- Viscum Album (Mistletoe)
- Scutellaria (Skullcap) & Valeriana Officinalis (Valerian)
- Jin Bu Huan (Chinese herbal tablets)
- Artemisia, hare’s ear, chrysanthemum, plantago seed, gardinia, red peony root, etc.


**Adverse Effects of CAM**

- Contamination: heavy metals, herbicides, pesticides
- Delayed side effects that go undetected: teratogenicity and carcinogenicity (HCC due to sassafras root in laboratory animals)
- Interaction with medicinals:
  - Chinese herbs & Coumadin
  - St. John’s Wort & Oral Contraceptive Steroids
  - St. John’s Wort & Cyclosporine
- 1% to 4% of admissions to Taiwan and Hong Kong hospitals might be related to adverse reactions to CAM
- Under-reporting of adverse effects

**St. John’s Wort & Cyclosporine**

Herb-Drug Interactions

- Garlic: Anticoagulants, ASA (bleed)
- Gingko Biloba: Anticoagulants, ASA (bleed)
- Ginseng: Warfarin (clot)
- Grapefruit juice: CSA, felodipine, itraconazole
- Kava: Benzodiazepines (sedate)
- Licorice: Diuretics, antiarrhythmics
- Ma Huang: MAO inhibitors, antihypertensives, caffeine, theophylline
- St. John’s Wort: CSA, digoxin, HIV protease inhibitors, theophylline, SSRIs
- Valerian: Barbiturates (sedate)