Esiste una tossicità epatica da Interferone?

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## Industry SAE Priorities 2006

**Rank Order [1 highest to 5 lowest]**

<table>
<thead>
<tr>
<th></th>
<th>Overall Priority</th>
<th>Variance</th>
<th>Your Company's Priority</th>
<th>Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatotoxicity</td>
<td>1.1</td>
<td>low</td>
<td>1.2</td>
<td>low</td>
</tr>
<tr>
<td>QT Prolongation</td>
<td>2.6</td>
<td>moderate</td>
<td>2.5</td>
<td>high</td>
</tr>
<tr>
<td>Rhabdomyolosis</td>
<td>3.3</td>
<td>moderate</td>
<td>3.5</td>
<td>mod</td>
</tr>
<tr>
<td>SJS</td>
<td>3.5</td>
<td>high</td>
<td>3.4</td>
<td>high</td>
</tr>
<tr>
<td>Edema</td>
<td>4.4</td>
<td>high</td>
<td>4.5</td>
<td>high</td>
</tr>
</tbody>
</table>

**SAE Consortium Survey – courtesy of Arthur Holden**
Why clinical drug development programs were terminated in 1991 and 2000

Nature Reviews: Drug Discovery, Aug, 2004
Drug Induced Liver Injury (DILI) can mimic every known liver disease

- Cholestasis (&vanishing bile duct syndrome)
- Steatosis (micro and macrovesicular)
- Phospholipidosis
- Veno-occlusive disease
- Occult fibrosis/ cirrhosis
- Liver cancer

**Acute hepatocellular injury** – High ALT/AST
“Hepatotoxicity has been the most common single adverse effect causing major drug problems, including withdrawals and refusals to approve”

Bob Temple, M.D.
FDA
2/15/01
## Regulatory actions due to DILI (1995-2006)

<table>
<thead>
<tr>
<th>Withdrawals</th>
<th>Second Line</th>
<th>Warnings</th>
</tr>
</thead>
<tbody>
<tr>
<td>bromfenac</td>
<td>felbamate</td>
<td>acetaminophen, leflunomide, nefazodone, nevirapine, pyrazinamide/rifampin, terbinafine, valproic acid, zifirlukast, atomoxetine, interferon 1β–1b and 1a, saquinavir, infliximab, bosentan, telithromycin (kava, lipokinex)</td>
</tr>
<tr>
<td>troglitazone</td>
<td>tolcapone</td>
<td></td>
</tr>
<tr>
<td>pemoline</td>
<td>trovafloxacin</td>
<td></td>
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</tbody>
</table>

[http://www.fda.gov/medwatch/safety.htm](http://www.fda.gov/medwatch/safety.htm)
Discovery of Interferons

• In 1957 Isaacs and Lindenmann did an experiment using chicken cell cultures
• They found a substance that interfered with viral replication and was therefore named interferon
• Nagano and Kojima also independently discovered this soluble antiviral protein
What are Interferons?

• Naturally occurring proteins and glycoproteins secreted by eukaryotic cells in response to viral infections, tumors, and other biological inducers
• Produce clinical benefits for disease states such as hepatitis, various cancers, multiple sclerosis, and many other diseases
• Structurally, they are part of the helical cytokine family which are characterized by an amino acid chain that is 145-166 amino acids long
Type I Interferons

• Type I: alpha and beta
• Alpha interferons are produced by leukocytes
• Beta interferons are produced by fibroblasts
• Both bind to interferon cell receptors type 1 and both encoded on chromosome 9
• They have different binding affinities but similar biological effects
• Viral infection is the stimulus for alpha and beta expression
• Used to mobilize our 1st line of defense against invading organisms
• Largest group and are secreted by almost all cell types
Type II Interferon (gamma)

- Bind to type 2 receptors and its genes are encoded on chromosome 12
- Initially believed that T helper cell type 1 lymphocytes, cytotoxic lymphocytes and natural killer cells only produced IFNg, now evidence that B cells, natural killer T cells and professional antigen-presenting cells secrete IFNg also.
- Gamma production follows activation with immune and inflammatory stimuli rather than viral infection.
- This production is controlled by cytokines secreted by interleukin 12 and 18.
Different Interferon Drugs

- **Recombinant forms of alpha interferon:**
  - Alpha-n3 drug name: Alfaferone®
  - Alpha-2a drug name: Roferon®, Pegasys®
  - Alpha-2b drug name: Intron A®, Pegintron®

- **Recombinant forms of beta interferon:**
  - Beta-1a drug name: Avonex®, Rebif®
  - Beta-1b drug name Betaseron®, Extavia®

- **Recombinant forms of gamma interferon:**
  - Gamma-1b drug name Imukin®
Side Effects of Interferon

- Headache
- Malaise
- Fever
- Chills
- Fatigue
- Myalgia
- Low Back Pain
- Joint Pain
- Nausea
- Anorexia
- Confusion
- Depression

% Patients
Indications for Interferon

- **Alpha**
  - *Hepatitis B & C*, Hairy cell leukemia, Chronic myeloid leukemia, multiple myeloma, low grade lymphomas, Kaposi’s Sarcoma, Melanoma

- **Beta**
  - Multiple Sclerosis, (Ulcerative colitis)

- **Gamma**
  - Chronic granulomatous disease, Chronic Myeloid Leukemia, Renal cell Carcinoma
Typical Acute Hepatocellular DILI leading to Death

Days on Study

Drugs

ALT
AST
ALP
TBL

ULN
3.2 xULN
10 xULN
32 xULN

death
jaundice
enceph
We propose that hepatitis may be due to an immune lysis of hepatocytes and suggest that this immune response may contribute to viral clearance.
Acute hepatitis induced by alpha-interferon in a patient with chronic hepatitis C

The most probable mechanism is an excessive immune response to HCV, but it is not clear whether this excessive immune response contributes to the elimination of HCV.

Can J Gastroenterol 2001
REVERSIBLE DECOMPENSATED LIVER DISEASE AS A POSSIBLE COMPLICATION OF PEGYLATED INTERFERON ALFA 2B AND RIBAVIRIN FOR RECURRENT HEPATITIS C

• A 36-year-old woman with cirrhosis caused by HCV underwent OLT.
• Liver biopsy was carried out 6 months later for elevated ALT and demonstrated recurrent HCV. The HCV genotype was 3a and the HCV-RNA viral load was 4.7 million copies/mL.
• She was started on a 6-month course of pegylated a-interferon 2b with ribavirin 800 mg/day.
• One month later she developed massive ascites, jaundice and renal failure. Pegylated IFN and ribavirin were immediately discontinued.
• Two months later her ascites had resolved completely with aggressive medical management.
• She remains asymptomatic and diuretics have been discontinued, but treatment for recurrent HCV has not been restarted.
Pegylated interferon alfa-2b* versus observation alone in resected stage III melanoma (Lancet 2008)

<table>
<thead>
<tr>
<th></th>
<th>Interferon group (N=608)</th>
<th>Observation group (N=613)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Any</td>
<td>605 (99%)</td>
<td>246 (40%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>574 (94%)</td>
<td>89 (15%)</td>
</tr>
<tr>
<td>Liver function test*</td>
<td>479 (79%)</td>
<td>64 (10%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>454 (75%)</td>
<td>24 (4%)</td>
</tr>
<tr>
<td>Headache</td>
<td>425 (70%)</td>
<td>24 (4%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>408 (67%)</td>
<td>22 (4%)</td>
</tr>
<tr>
<td>Depression</td>
<td>360 (59%)</td>
<td>38 (6%)</td>
</tr>
</tbody>
</table>

*6 µg/kg per week for 8 weeks (induction) then 3 µg/kg per week (maintenance) for an intended duration of 5 years.
Primary biliary cirrhosis induced by interferon-alpha therapy for hepatitis C virus infection

Exacerbation of primary biliary cirrhosis during interferon-alpha 2-b therapy for chronic active hepatitis C
Hepatic Sarcoidosis Associated with Pegylated Interferon Alfa Therapy for Chronic Hepatitis C: Case Report and Review of the Literature

Mohathi Adla - Kathy K. Downey - Jawad Ahmad

Pre-Tx
Mild portal inflammation

14 weeks Tx
Poorly formed granuloma

2 mo. after Tx
well-formed granuloma
ALT elevations reported in pre- and post-marketing studies of beta-interferons for multiple sclerosis

<table>
<thead>
<tr>
<th>Pivotal clinical trial</th>
<th>Time period; patient numbers</th>
<th>Definition</th>
<th>Patients affected</th>
<th>Post-marketing studies or re-analysis of clinical trial data</th>
<th>Time period; patient numbers</th>
<th>Definition</th>
<th>Patients affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFNB-1a (im; 30mcg weekly)</td>
<td>2 years; n = 158 [39]</td>
<td>'no evidence of liver enzyme elevations'</td>
<td>–</td>
<td>1) mean 1.3 years; n = 52 [41] &gt; UNL</td>
<td>1) 23%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFNB-1b (sc; 250mcg alt. days)</td>
<td>2 years; n = 124 [58]</td>
<td>'mild or moderate'</td>
<td>11%</td>
<td>1) year, n = 156 [59] &gt; UNL</td>
<td>1) 38%*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFNB-1a (sc; 22mcg 3/wk)</td>
<td>2 years; n = 177 [40]</td>
<td>'increased'</td>
<td>20%</td>
<td>1) mean 1.2 years; n = 128 [41] &gt; UNL</td>
<td>1) 34%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFNB-1a (sc; 44mg 3/wk)</td>
<td>2 years; n = 179 [40]</td>
<td>'increased'</td>
<td>27%</td>
<td>1) mean 1.2 years; n = 129 [41] &gt; UNL</td>
<td>1) 38%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>1) 2 years; n = 123 [58] 2) 2 years; n = 187 [40]</td>
<td>1) 'mild or moderate at some time' 2) 'increased'</td>
<td>1) 4% 2) 1.1%</td>
<td>2 years; n = 392 [37] &gt; UNL</td>
<td>2) 67%</td>
<td></td>
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</tr>
<tr>
<td>Baseline (pre-treatment)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1) 1 day; n = 152 [59] &gt; UNL</td>
<td>1) 5%</td>
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<td></td>
<td></td>
<td></td>
<td>2) 1 day; n = 724 [41]</td>
<td>2) 5%</td>
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<td></td>
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<td>3) 1 day; n = 624 [37]</td>
<td>3) 10%</td>
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</tbody>
</table>
Severe Acute Hepatitis After Resumption of Interferon-Beta Therapy for Multiple Sclerosis: A Word of Caution

Grieco et al. 2007

hemorrhagic centrilobular necrosis and inflammatory infiltrate.
Conclusions

• A very large number of patients are treated with IFN, but only a very small number of them develop toxic effects.

• IFN hepatotoxicity can be the result of the drug’s direct effects on liver tissue by inhibition of cytochrome p450 activity, or the manifestation of an autoimmune phenomenon.

• In chronic C hepatitis liver damage may occur as a consequence of exaggerated immune response to HCV.