Lessons from the Partner Study

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Biologics and Viral Hepatitis
Biologic Agents: An Ever Expanding List

- Anti-TNF (Infliximab, Etanercept, Adalimumab)
- Anti-CD20 monoclonal antibody (Rituximab)
- Selective antibodies against adhesion molecules — Natalizumab, MLN-02, Alicaforsen
- Anti-IFN gamma
- Anti-IL-12
- Anti-CD3 (Visiluzimab)
- Anti-CD25
- Anti-IL-6R (Tocilizumab)

Cytokines in Liver Disease
Anti-TNF and Liver Toxicity: Clinical Trials Data

Proportion of Patients with Elevated ALT in Clinical Trials

<table>
<thead>
<tr>
<th>Condition</th>
<th>&gt;1 to &lt;3 x ULN</th>
<th>≥3 x ULN</th>
<th>≥5 x ULN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>REMICADE</td>
<td>Placebo</td>
</tr>
<tr>
<td>RA a</td>
<td>24%</td>
<td>34%</td>
<td>3%</td>
</tr>
<tr>
<td>Crohns b</td>
<td>34%</td>
<td>39%</td>
<td>4%</td>
</tr>
<tr>
<td>UC c</td>
<td>12%</td>
<td>15%</td>
<td>1%</td>
</tr>
<tr>
<td>Ankyl spondyl d</td>
<td>13%</td>
<td>40%</td>
<td>0%</td>
</tr>
<tr>
<td>Psoriaticarthr e</td>
<td>16%</td>
<td>42%</td>
<td>0%</td>
</tr>
</tbody>
</table>

a Placebo patients received methotrexate while REMICADE patients received both REMICADE and methotrexate.
b Patients who were randomized to the placebo maintenance group and then later crossed over to REMICADE are included in the REMICADE group in ALT analysis.
c Median follow-up for all trials was 18-58 weeks.
Chronic Viral Hepatitis

- Chronic Hepatitis C (HCV)
- Chronic Hepatitis B (HBV)

Hepatitis C Virus: An RNA virus!

- Envelope
- Core
- Envelope Glycoproteins
- Viral RNA (9400 nucleotides)

55-65 nm
TNF Levels in Patients with HCV are increased

- Elevated TNF levels documented HCV infection\(^1\)-\(^3\)
  - Patients with chronic HCV with steatosis have shown higher levels of TNF\(^4\)

HCV Treatment Response and TNF

• Response to therapy may correlate to TNF levels\(^5\)
  – TNF levels may be beneficial in treating HCV infection

HCV Viral Kinetics During IFN Therapy

- **Phase 1**: Direct antiviral effect
- **Phase 2**: T-cell mediated elimination of infected hepatocytes

Cope AP, J Clin Invest 1994

- **Control**
- **High Concentration TNF**
- **Anti-TNF exposure**
Liver Elimination of HCV-infected hepatocytes

IFN-γ

Inhibition of T-cell activation

APC

Th1

HCV

TNFA

Macrophage activation

TNFA and IR

TNF-α

TNFR

JNK

IKK

IRS-1

AP-1

NF-κB

↑ Inflammatory mediators

Insulin Action

Feldstein AE and Zein NN. Am J Gastro 2008
HCV core protein and IR: Experimental Model

HCV core protein
Transgenic mice

Treatment with TNFA antibodies

Hepatic IR

High TNFA

Normal mice

No IR


Phase II Study: TNF Antagonist as Adjuvant Therapy in Patients with HCV Infections

R
N=50

Etanercept, interferon, ribavirin (n=19)

Placebo, interferon, ribavirin (n=25)

Zein NN for the Etanercept Study Group. J Hepatol. 2005
Results

Primary end points

- No liver toxicities were identified in this trial
- No increase in the frequency of adverse effects between the etanercept and placebo groups.
- Most adverse effects were LESS frequent in the etanercept group.

Toxicity

*P=0.04 vs. control.
The Partner Study an the Lessons…

AIMS

• Investigate whether the addition of infliximab to standard regimen of Peg IFN alpha-2b/RBV:
  —Improves SVR (primary)
  —Decreases fibrosis
  —Improves safety profile
Design

• Randomized, blinded, controlled, multi-center efficacy and safety study

• Total subjects: 150 from 10 sites (15 patients per site).

• Interim analysis after 50% of subjects complete 6 months of study.

The Partners in the Partner Trial

- Zein
- Post
- Mullen
- Jacobson
- Reddy
- Hemeidan
- Poordad
- Hassanein
- Gharib
- El-Serag
Design

Randomize 1:1
Stratify by Viral Load
And Ethnicity

Naïve
Genotype 1

SOC + Placebo

Interim Analysis
at 24 weeks

SOC + Infliximab

ADD 20 NRs
In 3rd, Open-Label
SOC + Infliximab arm

48 weeks
treatment

Primary endpoint
SVR @ 72 weeks
Secondary endpoint
Fibrosis on biopsy @ 72 weeks

Primary End Point

• SVR: non-detectable HCV RNA (< 29 IU/mL, real-time PCR assay) at week 72.
FDA Postmarketing hepatotoxicity with TNF inhibitors

• July 8th 2003 FDA drug safety database searched for all AEs of liver toxicity with infliximab, etanercept, adalimumab
  
  - Infliximab 799
  - Etanercept 402
  - Adalimumab 74

• July 9, 2004 AERS was searched for cases of severe liver injuries especially hepatic failure and cirrhosis
  
  - Infliximab 110
  - Etanercept 41
  - Adalimumab 7
FDA Postmarketing hepatotoxicity with TNF inhibitors

• Specific ‘Liver Failure” cases were further identified With or without supporting information Liver related signs/symptoms i.e. CNS, OLT,,death,Injury and impaired function with CNS, renal or coagulopathy
  – Infliximab 71
  – Etanercept 26
  – Adalimumab 4

FDA Postmarketing hepatotoxicity with TNF inhibitors

• Rigorous Exclusion for causality and reliability
  – Infliximab 19
  – Etanercept 8
  – Adalimumab 3
Disposition of Patients

N=220
Patients Screened

N=149
Patients Randomized

N=146
Patients receiving medication

N=73
Placebo

N=56
Completed 72 weeks

N=17
Discontinued before 72 weeks

N=73
Infliximab

N=45
Completed 72 weeks

N=28
Discontinued before 72 weeks

Results

• SVR rates were identical in both study arms (36%-38%) and were no different for what has been published in clinical trials of PEG/RBV

• No differences in AEs or SAEs between the two study arms.
• No safety concerns
• As for efficacy:
  – Phase 2 vs. phase 3 clinical trials?
  – Etanercept vs. Infliximab?