HDV Therapies

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Why Treat?

• Decrease death
• Decrease HCC
• Decrease Cirrhosis
• HBsAg seroconversion
• HDV RNA loss

• 25% HBsAg-positive liver transplant recipients in Europe are HDV positive
  • Rizetto et al J Hepatol 2021
Challenges

• Few targets
• Host responsible for replication
• Cell to cell spread
• HBV integration
• Virology at its simplest yet most daunting
  • Essentially RNA with a ribozyme

• HBV suppression is common in HDV infection
• HBV elimination is the goal
Further Challenges

• Often advanced disease
  • Flares on treatment
  • Flares on withdrawal of treatment

• HDV suppression associated with HBV flares

• Standardization of testing

• Standardization of responses

• Is it really relapse or is it insensitive assays?

• Lack of awareness

• Confusion with autoimmune hepatitis
Vaccination for Hepatitis B is the Ultimate Cure

Eradication of Hepatitis D!
Future Therapies Reflect the Successes of Molecular Virology and Cell Biology

• Understanding the HDV lifecycle has revealed opportunities

Hercun et al, Gastroenterol Clin North Am, 2020
History


**Treatment of chronic delta hepatitis with recombinant human alpha interferon.**


PMID: 3628383 [PubMed - indexed for MEDLINE]

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**Alpha 2 recombinant interferon in the treatment of chronic hepatitis delta virus (HDV) hepatitis.**

Rosina F, Saracco G, Lattore V, Quartarone V, Rizzetto M, Verme G, Trinchero F, Sansalvatore F, Smedile A.

PMID: 3628384 [PubMed - indexed for MEDLINE]
Interferon, Good News

• 41 patients, 48 weeks, IFN α
  • 9 MIU TIW vs 3 MIU TIW vs No therapy

<table>
<thead>
<tr>
<th></th>
<th>9 MIU</th>
<th>3 MIU</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochemical</td>
<td>71%</td>
<td>29%</td>
<td>8%</td>
</tr>
<tr>
<td>Virological</td>
<td>71%</td>
<td>36%</td>
<td>0%</td>
</tr>
<tr>
<td>Complete</td>
<td>50%</td>
<td>21%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Interferon, Bad News

- Long term response
  - Zero out of 41!!!

- Conclusion: “However, a relapse is common after treatment has been stopped.”
Interferon, Good News

• Longer follow up of 36 of the previous patients
• Survival statistically in favor of high dose vs low dose and high dose vs controls
• ALT normal in 7/12, 2/4, and 0/3 in the 3 groups respectively
• Regression of cirrhosis in 4 patients

Farci P et al Gastroenterology 2004
Proof of Concept - Lau et al, Gastroenterology 1999

• Resolution of chronic delta hepatitis after 12 years of interferon alfa therapy.
  • Resolution of cirrhosis!
## Interferon Trials for HDV

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>Patient Number</th>
<th>SVR 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farci et al 1994 NEJM</td>
<td>IFN 9 MIU vs 3 MIU vs No Therapy 12 months</td>
<td>41</td>
<td>0%</td>
</tr>
<tr>
<td>Gunsar et al 2005 Antivir Ther</td>
<td>IFN vs IFN+RBV x 24 months</td>
<td>31</td>
<td>20 vs 24%</td>
</tr>
<tr>
<td>Castelnau et al 2006 Hepatology</td>
<td>PEGIFN x 12 months</td>
<td>14</td>
<td>43%</td>
</tr>
<tr>
<td>Niro et al 2006 Hepatology</td>
<td>PEGIFN vs PEGIFN+RBV x 18 months</td>
<td>38</td>
<td>25 vs 18%</td>
</tr>
<tr>
<td>Heller et al 2014 Aliment Pharmacol Ther</td>
<td>PEGIFN at escalating doses to 360 ug/wk for 5 years</td>
<td>13</td>
<td>23%</td>
</tr>
</tbody>
</table>
Durable Virologic Response and Functional Cure of HDV with Long-term Peginterferon

- 12 patients > 6 months
- 6.1 years of therapy (0.8 – 14.3)
- Follow up 8.8 years (1.7 – 17.6)
- 7 undetectable HDV RNA
- 6/7 responders alive
- 4 HBsAg loss
- 1/5 non-responders alive

Hercun et al., Aliment Pharmacol Ther. 2021 Jul;54(2)
More Problems

• All small studies
• Limited experience with different genotypes
  • Mostly 1
• Different HDV RNA assays
• Different doses, duration, follow up, and end points
## Anti HBV Therapies for HDV

<table>
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<th>Trial</th>
<th>Treatment</th>
<th>Patient number</th>
<th>SVR 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lau et al 1999 Hepatology</td>
<td>LAM x 12 months</td>
<td>5</td>
<td>0%</td>
</tr>
<tr>
<td>Yurdaydin et al 2008 J Vir Hepat</td>
<td>LAM vs IFN and LAM vs IFN</td>
<td>39</td>
<td>12% vs 36% vs 50%</td>
</tr>
<tr>
<td>Wedermeyer et al 2011 NEJM (HIDIT-1)</td>
<td>PEG vs PEG and ADF vs ADF x 48 weeks</td>
<td>90</td>
<td>31% vs 26% vs 0%</td>
</tr>
<tr>
<td>Wranke et al 2014 PLOS one (HIDIT-2)</td>
<td>PEG vs PEG and TDF x 96 weeks</td>
<td>120</td>
<td>21% vs 29%</td>
</tr>
</tbody>
</table>
Treatment Guidelines?

• No current FDA approved therapy for HDV.

• AASLD:
  • “PegIFN alpha for 12 months is the recommended therapy for those with elevated HDV RNA levels and ALT elevation”
  • ”If HBV DNA levels are elevated, concurrent therapy with NA using preferred drugs is indicated.”
  • “Given the limited efficacy of current therapies, it is reasonable to refer patients to specialized centers that offer access to experimental therapies for HDV.”

Terrault et al. Hepatology 2018
Investigational Treatment Options

• New therapies
  • Pegylated-IFNλ
  • Entry inhibitors (Bulevirtide)
    • EMA approved
    • Orphan drug status in the US
  • Nucleic acid polymers – REP-2139 (Replicor©)
  • Prenylation inhibitors (Lonafarnib)
    • Orphan drug status in the US
Caveat

• Much of the data has only been presented in abstract form
• Much of the data is dose, duration, and optimal administration discovery
• Will focus on highlights
• Surrogates (remember why we treat):
  • ALT
  • > 2 log HDV decline
  • What is a durable virologic response?
    • Yurdaydin C et all, J Hepatol 2019
Peginterferon Lambda

- Type-III Interferon
  - Receptors greater hepatic restriction.
  - JAK/STAT pathway – similar to IFN alpha
  - Similar efficacy in HBV and HCV with less side effects

Foster et al. Springerplus 2016.
Peginterferon Lambda Clinical Trials in HDV

• Phase 2 Lambda Monotherapy Study (LIMT)
  • 36 subjects
  • 120 vs 180 mcg SQ weekly
  • 48 weeks of therapy
• At 24 weeks of post-therapy follow-up
  • 36% Undetectable HDV RNA
  • 36% ALT normalization
• 6 patients elevated Bilirubin
  • Resolved in all

Etzion et al., J Hepatol 2019;70, e32.
Lifecycle

Hercun et al, Gastroenterol Clin North Am, 2020
HBV Entry Inhibitors

- Human sodium-taurocholate co-transporter peptide (hNTCP)
  - Transmembrane protein receptor for HBV & HDV
  - Inhibits HBV & HDV entry in *in vivo* models

Bogomolov et al., J Hepatol 2015
Bulevirtide

• Phase 1b/2a, 3-arm parallel, open-label POC study.
  • 24 patients: MyrB 2mg
  • MyrB vs MyrB+PegIFN vs PegIFN x 24 weeks
  • HDV RNA Decline: -1.67, -2.6, -2.2 log10 IU/ml

• Phase 2b, open-label study
  • 120 patients
  • 2, 5, 10 mg x 24 weeks
  • Max decline @ 10 mg: -2.7 log10 IU/ml

• Phase 2b, Multicenter, Open-labeled, Randomized
  • 60 patients
  • 2, 5 mg MyrB +/- PegIFN alfa 2a x 48 weeks
  • EOT-Undetectable HDV RNA: 53% (2 mg), 27% (5 mg)

Bogomolov et al., J Hepatol 2016
Wedemeyer et al., J Hepatol 2018
Bulevirtide Monotherapy at Low and High Doses in Patients With Chronic Hepatitis Delta: 24-Week Interim Data of the Phase 3 MYR301 Study

Methods

Study Design

Interim analysis

Primary endpoint: combined response
- Undetectable HDV RNA or decrease by ≥2 log₁₀ IU/mL from baseline
- Normal ALT

Week 0

24

48

144

240

N=150 randomized 1:1:1, stratified by liver cirrhosis status

n=51

No treatment

BLV 10 mg sc qd*

Follow-up

n=49

BLV 2 mg sc qd*

n=50

BLV 10 mg sc qd*

*Nucleos(t)ide analogues for treatment of underlying HBV infection were allowed if indicated by treatment guidelines.

Wedemeyer et al, EASL 2021
Results

**Changes in HDV RNA Over Time**
- Compared with no treatment, BLV led to a decline in HDV RNA, with similar rates of HDV RNA decline with BLV 2 and 10 mg over 24 wk of treatment.

**ALT Normalization Over Time**
- After 24 wk of treatment, rapid ALT reduction and normalization were observed in >50% of patients in the BLV 2-mg arm.

**Virologic and Biochemical Responses at Week 24**

- **Combined Response**
  - Undetectable HDV RNA or \(2\log_{10}\) IU/mL Decrease From Baseline and Normal ALT

- **Virologic Response**
  - Undetectable HDV RNA or \(2\log_{10}\) IU/mL Decrease From Baseline

- **ALT Normalization**

* *<0.001. CI: confidence interval.*

Wedemeyer et al, EASL 2021
HBsAg Secretion Inhibitors

- Nucleic acid polymers (NAPs)
- Phosphorothioated oligonucleotides with activities against a diverse array of infectious agents.
  - HSV
  - Arenaviruses
  - HCV
- Specific mechanisms of action still unknown.

Beilstein et al., J Virol 2018
Boulon et al., Antivir Res 2020
Matsumura et al., Gastroenterology 2009
Nucleic Acid Polymers (NAPs)

- REP2139-Ca
- 12 patients
- 500mg IV x15 weeks -> 250 mg IV + PegIFN alpha x 15 weeks -> PegIFN alpha x 33 weeks.
- Mean HDV RNA decline: 5.34 log 10 IU/ml
- ETR 75% HDV RNA negative, 83.3% > 2 log decline
- ETR 42% HBsAg negative
- 1 year 5 (58%) HDV RNA negative
- 3.5 year 4 HDV RNA negative
- 1 AE decompensation but recovered

Bazinet et al., Lancet Gastroenterol Hepatol 2017
Viral Assembly & Packaging Inhibitors

- Prenylation
- Post-translational lipid modification involving the covalent addition of prenyl lipids to proteins
- Promotes membrane interactions
- Promotes biological activities of a variety of cellular proteins

Bordier et al., J Virol 2002
Glenn et al., J Virol 1998
Lonafarnib Monotherapy for 28 Days

Lonafarnib for HDV

• GI Side Effects
  • Nausea
  • Diarrhea
  • GERD
  • Weight loss

• How do we improve GI tolerability while maintaining serum drug levels?
  • CYP3A4

Ritonavir (green) bound to the active site cavity of CYP3A4. Sevrioukova IF, et al. PNAS 2010;107
18-DK-0123: Treatment of Chronic Delta Hepatitis with Pegylated Lambda Interferon, Lonafarnib & Ritonavir

• Lambda InterFeron combination Therapy: Phase 2a, Open-Label Study for 24 weeks with 24 weeks follow up
  • Peginterferon lambda (LMD) 180 mcg subcutaneously weekly
  • Lonafarnib (LNF) 50 mg orally twice daily
  • Ritonavir (RTV) 100 mg orally twice daily

• Primary Endpoints:
  • Therapeutic: >2 log decline in quantitative HDV RNA levels after 24 weeks of therapy
  • Safety: Ability to tolerate triple combination therapy at the prescribed dose for 24 weeks.

Koh C et. al., The Liver Meeting, Oct 30, 2020
HDV RNA Change from Baseline to End of Therapy

Koh C et. al., The Liver Meeting, Oct 30, 2020

- 77% of patients achieved >2 log HDV RNA decline after 24 weeks of therapy.
- 50% had undetectable or BLOQ* HDV RNA after 24 weeks of therapy.
- 23% (5) patients remain below the LOQ at 24 weeks follow up

*Lower limit of quantification of HDV RNA in serum: <40 IU/mL or 1.6 Log, Quest Diagnostics Assay
## Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Hyperbilirubinemia</th>
<th>Anemia</th>
<th>Ascites</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose Reduction</strong></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Discontinuation</strong></td>
<td>4</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

Koh C, et al. J Hepatol. 2020, 73, S1
Summary

• Interferon is suboptimal
  • But wonderful for responders
• Suppress HBV to prevent flares, not improve outcomes
• Science reveals opportunities
  • Combinations, dose, duration, endpoints in progress
• BUT: The sun will come out tomorrow!
Thank you

• Chris Koh
• Jay Hoofnagle
• Jake Liang
• Jeff Glenn
• Harel Dahari
• Patients
• Fellows
• Nurses
• Eiger

Lau et al, Gastroenterology 1999