Clinical Update on Reducing HBV Virus and Antigen Production Using RNAi

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Disclosures

• Dr. Given is an employee and shareholder in Arrowhead Pharmaceuticals, Inc.
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RNAi: Target the Gene Silence the Disease

Therapeutic gene silencing with RNA interference is highly precise and efficient
A Very Simplified View of the HBV Lifecycle
• 5 viral mRNAs
  • 3.5 kb pre-genomic RNA
  • 3.5 kb pre-core mRNA
  • 2.4 kb pre-S1 mRNA
  • 2.1 kb pre-S2/S mRNA
  • 0.7 kb X mRNA

• 7 major proteins
  • Polymerase (with reverse transcriptase function)
  • Core (HBcAg), forms capsid
  • e antigen (HBeAg), also called pre-core, a secreted protein
  • Large, medium and small surface proteins (HBsAg), form envelope
  • X protein (Transactivator)

Same polyadenylation signal for all mRNAs

Ghany & Liang (2007), Gastroenterology 132: 1574-1585
RNAi Therapeutics to Reduce HBV Viral RNAs
Differentiation from nucleos(t)ide reverse transcriptase inhibitors
RNAi Can Reduce all cccDNA-derived Viral Antigens

- Synergistic effect with NUCs on DNA
- Contemporaneous reductions in HBeAg, HBcrAg, HBV RNA (not shown here)
Differences in Degree of HBsAg Reduction Correlated with HBeAg Status in Chimpanzees
ARC-520 in Treatment-naïve Chronic HBV Patients: Human HBsAg data reflects chimp data

- High level knockdown of HBsAg in HBeAg positive patients
- HBeAg negative patients respond less well
- HBeAg transitional patient is intermediate

As in chimps, HBeAg negative patients likely produce significant amounts of HBsAg from integrated DNA not targeted by ARC-520.

4 mg/kg ARC-520: NUC-naïve chronic HBV patients
1. HBV DNA integrates into host chromosome, during which regions between DR2 and DR1 can be randomly deleted (not new!)

2. Significant HBsAg mRNA can be produced from integrated HBV DNA
   - These S transcripts contain complete HBsAg CDS
   - Expected loss of ARC-520 target sites in many
• Subcutaneous dosing, monthly or less frequent
• No need for active endosomal escape agent
• **Addresses full HBV transcriptome**
  • Works for cccDNA and integrated-derived transcripts
• Multiple triggers to avoid resistance development
• Powerful HBsAg reduction
• Wide therapeutic index
• Efficacy and safety in HBV patients
Importance of Integrated HBV DNA as S mRNA Source has Changed RNAi Strategy

- Single siRNA can reduce all mRNA from cccDNA but can miss integrated HBV-derived mRNA
- Combination of X and S triggers → ARO-HBV
  - Greater genome coverage (99.6% full match of 17mer in ~7000 HBV genomes)
  - Reduce chance of resistance
HBsAg Reduction with ARO-HBV After 3 monthly Doses
Includes cohorts with complete data through 14 days after 3rd dose

See AASLD late-breaker poster Nov 12, 2018 for expanded and updated data
# CHB patient AE Table

**AEs in >1 subject (data cut 8/24/2018)**

<table>
<thead>
<tr>
<th>AROHBV1001 HBV Patients</th>
<th>Cohort 2b, 100mg X3 Q28 days</th>
<th>Cohort 3b, 200mg X3 Q28 days</th>
<th>Cohort 4b, 300mg X3 Q28 days</th>
<th>Cohort 5b, 400mg X3 Q28 days</th>
<th>Cohort 6, 100mg X3 Q2 wk</th>
<th>Cohort 7, 100mg X3 Q28 day</th>
<th>Cohort 8, e+ 300mg X3 Q28 day</th>
<th>Cohort 9, e+ 300mg X3 Q28 day</th>
<th>Cohort 10, 200mg X3 weekly</th>
<th>Cohort 11, 300mg X3 weekly</th>
<th>Total AEs</th>
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<tbody>
<tr>
<td>AE Reported Terms</td>
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<td>Insect bites ankles, Flea bites on neck</td>
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<td>Upper respiratory tract infection, Sore throat, Laryngitis, Dry cough</td>
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<td>3</td>
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<td>Erythema around injection sites, Injection site redness, Haematoma at injection site, Injection Site Bruise</td>
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<td>Headache, headache – intermittent</td>
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<td>Raised Creatine kinase</td>
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<tr>
<td><strong>TOTALS</strong></td>
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</tbody>
</table>
• Activity demonstrated in all patient types (HBeAg pos/neg, NUC naïve/treated)

• Response appeared to be independent of starting HBsAg levels

• ARO-HBV appeared to be generally well-tolerated as of the data cutoff (August 24, 2018)
  • Injection site reactions were observed in approximately 10% of injections
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