RNAi: Pulling Us Toward Finite Therapy

The Science of HBV Cure 2019
Singapore, June 7-8, 2019

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COO, Arrowhead Pharmaceuticals
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Simplified theories for an HBV RNAi therapeutic

1. "HBsAg Theory"
   - Reducing HBsAg enables host immune system de-repression and long term control of virus

2. Destabilizing Viral Function
   - Silencing all antigens and reducing pgRNA could destabilize normal viral function
   - Enable host immune system de-repression and long term control of virus
JNJ-3989 (ARO-HBV): Key design elements

- Addresses full HBV transcriptome
  - Two hepatocyte targeted RNAi molecules
  - Works for cccDNA and integrated-derived transcripts
  - Previously shown to reduce HBV DNA, HBV RNA, HBsAg, HBeAg, & HBcrAg $^{1,2}$
- Multiple triggers to avoid resistance development and increase coverage of viral genomes

Patients receiving 3 monthly doses have achieved > 1 log reduction in HBsAg

Mean HBsAg reductions from baseline

- NADIR in HBsAg is reached around 4 months post start of therapy
- Duration of pharmacologic effect persisted for > 4 months after last dose

Yuen MF et al. ILC 12 April 2019, PS-080 (as of 2/28/2019)
Individual HBV DNA and RNA Responding Well

Colors in graphs indicate cohorts as follows: Red (C2b), orange (C3b), purple (C4b), green (C5b), black (C8), brown (C9)

The Science of HBV Cure, June 2019
Individual HBeAg and HBcrAg Also Showing Response

Colors in graphs indicate cohorts as follows: Red (C2b), orange (C3b), purple (C4b), green (C5b), black (C8), brown (C9)

The Search for HBV / HDV Cure 2018
## AEs reported in ≥ 2 CHB patients

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<th>AROHBV1001 HBV Patients</th>
<th>Cohort 2b Open Label n = 8</th>
<th>Cohort 3b Open Label n = 8</th>
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<th>Cohort 5b Open Label n = 8</th>
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64 Total

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Yuen MF et al. ILC 12 April 2019, PS-080 (as of 3/8/2019)
Early insights for JNJ-3989 plus NUC effects

• Strong activity against HBsAg and other viral products (when measurable)
  • Regardless of HBeAg status, prior NUC exposure or genotype

• Tolerability profile looking favorable
  • Mild injection site reactions most prominent (about 10% of injections)
  • No dropouts due to AEs or severe AEs
  • 2 non-drug related SAEs to date (menorrhagia and anxiety with depression)

• Current data is for 3 doses only
  • Longer treatment durations and combination therapy eagerly awaited
What else merits some discussion / thought?
Is on-treatment HBsAg level important for HBsAg seroclearance?

HBsAg levels of <100 IU/mL and HBsAg reduction of > 1 Log10 IU/mL have been associated with increased probability of HBsAg seroclearance after cessation of NUCs in HBeAg negative patients.  

1 Jeng et al. 2018 Hepatology 68:425-434
Distribution of quantitative HBsAg pre and post 3 doses of JNJ-3989

Baseline
Median: 1263 IU/mL
Min: 7.0 IU/mL
Max: 392,800 IU/mL

NADIR
Median: 14.5 IU/mL
Min: 0.05 IU/mL
Max: 8950 IU/mL

Red Points: HBeAg positive patients
Black Points: HBeAg negative patients

3 patients < 100 IU/mL

Yuen MF et al. ILC 12 April 2019, PS-080
Case study 1: Naïve HBeAg Negative Patient with HBsAg Seroclearance After ARC-520

- >2.4 Log10 HBsAg reduction from baseline to BLOQ (HBsAg seroclearance)
- HBcrAg BLOQ throughout the study
- HBV RNA decreased rapidly from a low baseline to BLOQ after single dose of ARC-520 and then remained at or below LLOQ throughout the study
- Rapid reduction of HBV DNA to undetectable levels with ARC-520 plus entecavir
- Antigen decrease and seroclearance off ARC-520 coincided with a doubling of ALT, consistent with increased host response to virus

Genotype: B2 adw
Case study 2: Naïve HBeAg Positive Patient with HBsAg Seroclearance After ARC-520

- HBsAg, RNA, HBeAg, HBcrAg all respond to a single dose of ARC-520
- Withdrawal of RNAi associated with host ALT response and reductions in viral parameters
- This patient ultimately serocleared 26 months after withdrawal of ARC-520
Some Informed Speculation (My Opinion Only)

• Finite therapy with Interferon and now NUCs has been associated with HBsAg seroclearance rates beyond spontaneous background
  • Often after a few years
• ARC-520 data even with background NUCs continuing looks similar to my eye
• JNJ-3989, representing the current generation of RNAi agents, can reduce all viral components and importantly might get HBsAg in most patients below 100 IU/ml
• True finite therapy, including stopping background NUCs, will be fascinating to watch in the next few years
  • Adding immune stimulation at this point only adds to the anticipation
Acknowledgements

• Patient volunteers
• Investigators, especially MF Yuen for long-term ARC-520 data
• Our Scientific Advisory Board (R. Gish, S. Locarnini, C. Ferrari, C.L. Lai)
• The Arrowhead Team
• Our Janssen colleagues