

Personalized Approach to HBV Therapy

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COI

- Spouse works for Hoffmann-La Roche

Personalized medicine

Definition: a medical procedure that separates patients into different groups—with medical decisions, practices, interventions and/or products being tailored to the individual patient based on their predicted response or risk of disease

- AKA precision medicine

Personalized medicine

We already do this in Hepatology

e.g. HCV- treatment differs depending upon

- HCV genotype
- Cirrhosis
- Decompensation
- Post transplant
- So how do we do for Chronic Hepatitis B?

The problem

- Vaccine available and successful
 - Not universal
 - Still many people with chronic HBV to manage
- Majority asymptomatic, many undiagnosed with
 - 25% death from ESLD, cirrhosis and HCC
 - Of those perinatally infected, up to 40% of men and 15% of women will die of liver cirrhosis or liver cancer without treatment

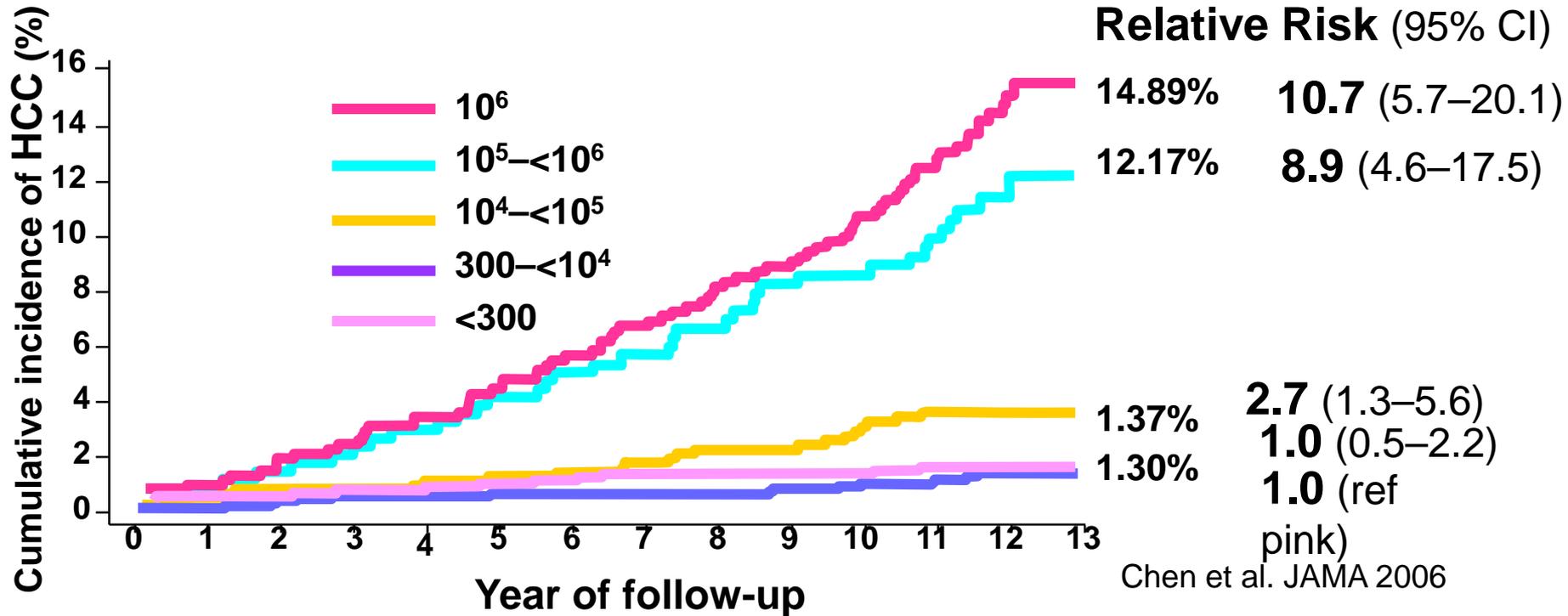
The problem

- Increased risk of progression/HCC shown in:
 - male sex
 - younger age of infection
 - Excess alcohol consumption, NAFLD
 - High hepatitis B DNA levels (over age 40 years)
 - Co-infections with HIV, HCV and HDV
 - Hepatitis B virus genotype C, Aa

Baseline HBV DNA and HCC

REVEAL study cohort 3,582

Age 45, Male 61%, ALT>45 6%, HBeAg-positive 15%



Risk of HCC in Chinese chronic HBV

Prospective follow-up of 22,707 Taiwan male civil servants

Status	Population at Risk	HCC	Relative Risk to HBsAg Negative Subjects
HBsAg negative	19,253 (84.8%)	3	–
HBsAg positive	3454 (15.2%)	113	217
• No cirrhosis	3414	107	201
• Cirrhosis	40	6	961

1. Beasley RP, et al. *Lancet*. 1981;2:1129.

2. Beasley and Hwang, *Viral hepatitis and liver disease* 1984; 209.

Types of HBV success to cure

Inactive state – “partial cure”

- No inflammation: normal ALT and liver biopsy
- HBV DNA u/d
- HBsAg positive

Functional Cure- clinical resolution Sustained, off Rx:

- No inflammation: ALT and liver biopsy
- HBsAg loss
- HBsAb gain

Complete cure- virological sterilizing cure

- All of above plus
- Loss of cccDNA in liver

Types of HBV success to cure

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Functional Cure- clinical

- No inflammation: ALT
- HBsAg loss
- HBsAb gain

Nature: Humans have
no HBV so no cccDNA

Complete cure- virological sterilizing cure

- All of above plus
- Loss of cccDNA in liver

Not an issue

- All patients with Chronic hepatitis B should be treated for a cure

Issue

- Will one size fit all?

2 HBeAg negative cases

66 yo female

- Rx 4-5y
- ALT
- Liver bx
- d/c Rx peak
- Outcome

ETV

20

F0-1

32

6000

lost HBsAg
anti-HBs pos (9mos)

32 yo male

TDF

25

F2

180 (b/r 2.1)

22,000,000

retreated TDF
still on Rx 2 yrs

2 Patients

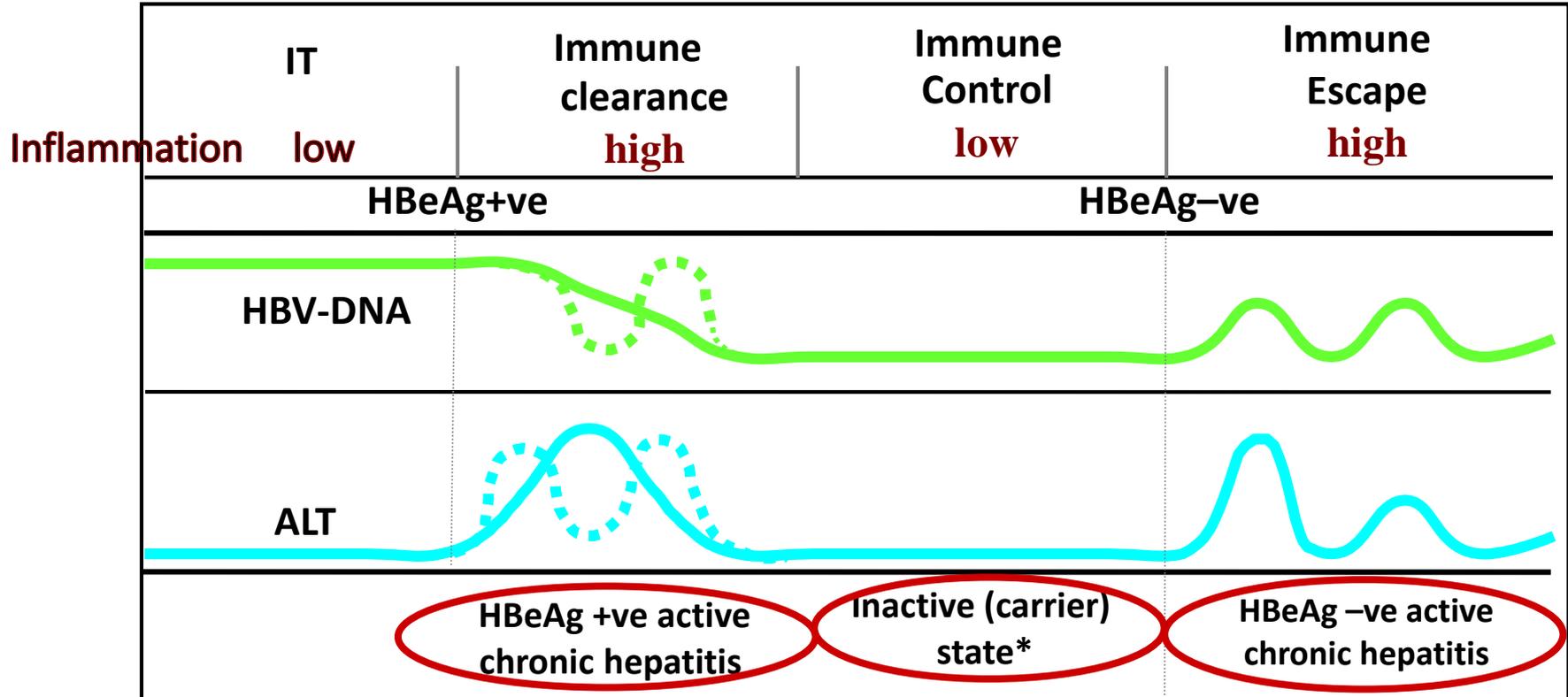
Why was the outcome different?

- Age
- Sex
- Pre Rx HBV DNA level
- Liver biopsy stage
- Other factors:
 - Viral
 - Immunological
 - Host, comorbidities, genetic

Chronic HBV: a dynamic heterogeneous disease

- Phases neither clear nor distinct
- Varying levels of HBsAg even in inactive patients
- Immunologic status between stages are fluid

The phases of chronic hepatitis B

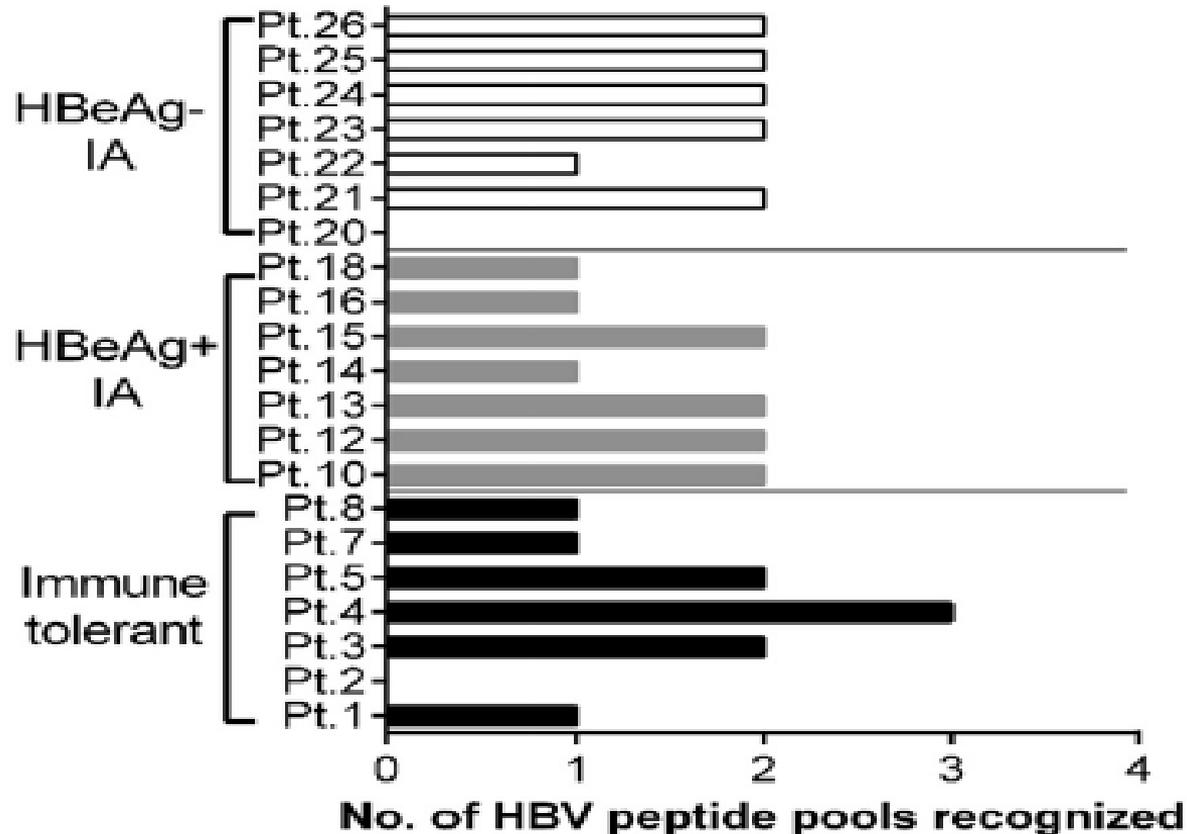


*Previously considered to be 'healthy carriers'

Chronic HBV: a dynamic heterogeneous disease

- Immunologic status between stages are fluid
- A high level of HBV-DNA integration and clonal hepatocyte expansion in young patients even in immune tolerant indicating that possible hepatocarcinogenesis even in patients with early stage CHB
- Similar “phases” have mixed responses
 - 9 IT pts only 2 had normal ALT- but core, pol, env did not distinguish phases

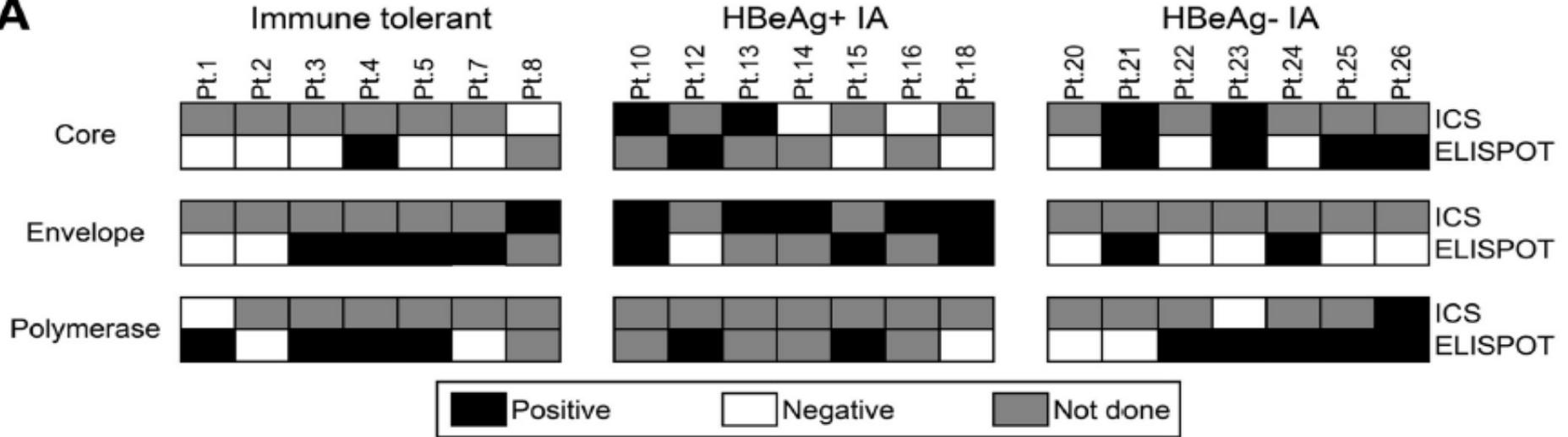
HBV peptides recognized in HBV Phases



IT #2#3

HBV-specific T-cell responses

A



HBsAg Epitope change during Rx

25 gA HBeAg positive patients on TDF differentiated

- 14 patients who demonstrated a HBsAg clearance profile (reduced recognition/availability at both loops 1 and 2 regions of the “a” determinant) and
- 11 patients with a non-clearance profile- no change in epitope recognition or reduced binding at only one epitope
- These HBsAg epitope changes positively correlated with HBsAg loss and anti-HBs sero-conversion ($P < 0.02$, PPV 83%)
- Clearance profile on antiviral therapy by week 24 or 48, was strongly associated with a significant decline (>1.0 log IU/ml) or loss in HBsAg

Phase of Disease: IT

- IT: Children/ young adults
 - Cure will provide the most benefit and most QALYs gained
 - Healthy, asymptomatic, busy with life
 - When is ideal time to treat
 - HBV DNA very high, ALT normal
- Studies show altered but measurable immune response and high viral load, not exhausted T cells
- Immune stimulant (PD-1, therapeutic vaccine) plus antiviral
- Will patients/parents accept hepatic flares?
- What s/e will patients/parents accept?

Phase of disease: Inactive

- Majority of HBV patients achieve this state
- Low or undetectable HBV DNA
 - <1% chance of clearing HBsAg per year
 - Lower risk of HCC than immune active
 - Lower risk of Cirrhosis and ESLD
- Exhausted or less differentiated T cell phenotype
- What HBV drugs will be needed to enhance clearance?
 - Will they need only immune stimulant or with DAA
 - E.g. Therapeutic vaccine

Phase of disease: Nuc Suppressed

- Patients already see some clinical benefit on nucs
 - Decreased inflammation, fibrosis progression and HCC incidence
- Many US patients want to stop drug
 - Will accept liver biopsy
- Others do not want to try new therapies
- These patients may be ideal to study “add on” therapies- e.g. antivirals

For HBV Cure studies

- Clinical benefit may take years to determine
- qHBsAg short term surrogate markers of efficacy. Are others needed to monitor success?
 - Immunologic
 - Virologic
 - Pathologic
- Which patients should and can we treat with new drugs?
 - Should patients be already suppressed on nucs?
 - Is risk/ benefit different depending on therapy, age of patient or phase of disease?
 - Do different phases need different therapies?

For HBV Cure studies

- Need rapid proof of concept and safety
- Early studies include patients
 - already suppressed on nucs
 - Immune active non cirrhotics
- Later studies:
 - Combination drugs
 - Do different phases need different therapies
- Easily available surrogate markers of efficacy
 - Must be from PBMC/ serum
 - Research studies should investigate liver and IR in depth

Strategies to Eradicate HBV

Virologic approaches

- Entry inhibitors
- Block cccDNA
- Transcription inhibitors
- RNA interference
- HBV capsid inhibitor
- polymerase inhibitors
- Secretion inhibitors

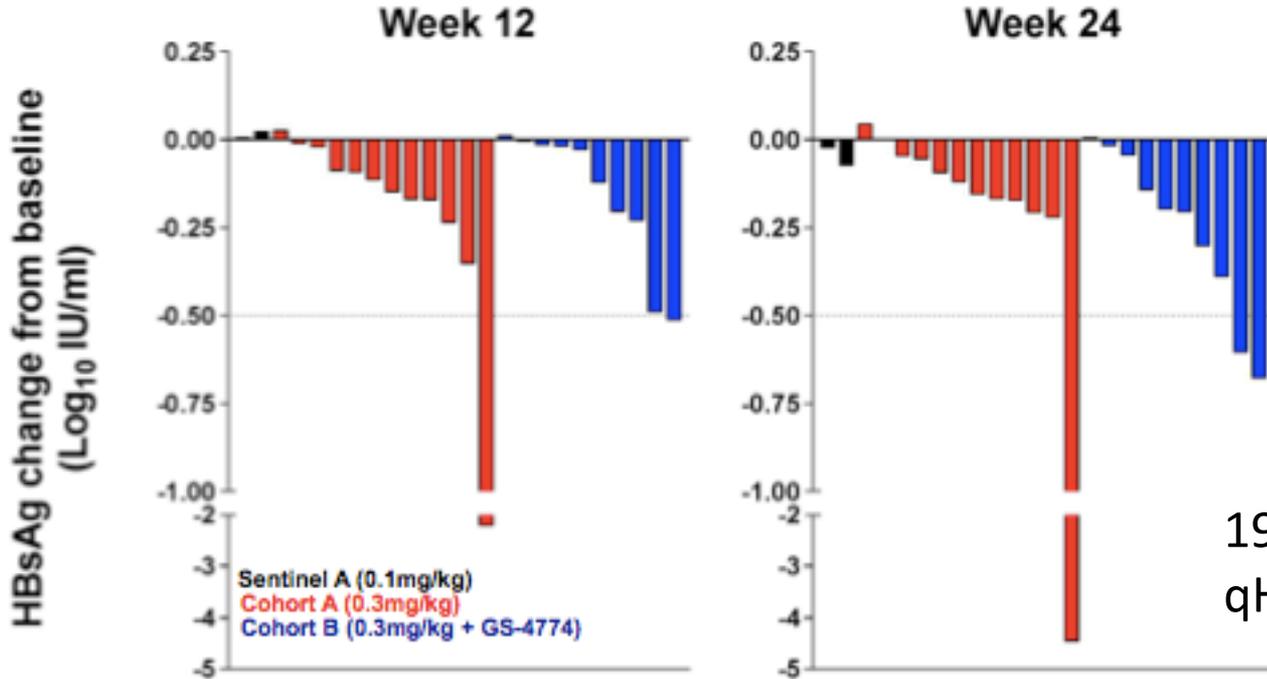
Host immune approaches

- Interferons
- TLR-7
- PD-1/ PDL-1
- IL-7
- Therapeutic vaccines
 - Immune complex vaccines
 - Nasal HBV (NASVAC) vaccines
 - DNA vaccines
 - T cell vaccines
 - Adenovirus based vaccines (TG1050)
 - Yeast based vaccines

HBV DAA in CHB AASLD 2017

- Bi-weekly Dosing of ARB-1467 LNP siRNA in HBeAg Neg, Virally Suppressed Patients with CHB Leads to Deeper Declines in HBsAg and Potential Association with IL28b. Agarwal et al
 - Bi-weekly dosing with ARB-1467 resulted in very low absolute levels of qHBsAg in 5/7 patients after 5 bi-weekly doses
- Safety, Tolerability, PK, and Antiviral Activity of JNJ-56136379, a Novel HBV Capsid Assembly Modulator, in Non-cirrhotic, Treatment-naïve CHB Patients. Zoulim et al.
 - 75 mg had 3 log decrease in HBV DNA over 4 weeks

qHBsAg change on anti-PD1 0.3mg/kg Nivolumab



240 mg IV
Q2w for
RCC, SC lung
Melanoma

ACTG

19/22 decreased
qHBsAg

How to determine what combination is required

- By age of patient
- By phase of disease
- By fibrosis stage
- By HBV genotype
- By clinical status

How to determine what combination is required

- By phase of disease
- By fibrosis stage
- By clinical status
- By age of patient
- Level of HBV DNA
- Level of HBsAg
- Activity of Immune Response
 - T cells exhausted
 - Ag spec T cells active
 - Cytokines
 - innate IR

New HBV markers HBcrAg, HBV RNA, cccDNA

Surrogate markers

Better markers needed to evaluate the efficacy

- if a drug is superior and/or complementary to current medications
- when therapy should be started, adjusted or stopped
- which patients will benefit most from a particular therapy

Surrogate marker: Time to virologic rebound

- <50% HBeAg positive patients rebound over several months but
- 70-80% of HBeAg negative patients rebound within weeks of drug withdrawal
- New therapeutics, provided as “add on” therapy to nuc controlled may prevent or significantly delay rebound of viremia when both stopped
- The “add on” values of a drug could be relatively quickly determined in HBeAg negative patients, since the time to rebound following cessation of nucs is short

Surrogate marker: Infected cell number

- Pre-drug, on drug and off drug infected cell numbers would be a very useful marker of efficacy
- Laser capture microdissection (focused laser with a fully automated light microscope) has been used to study single hepatocytes in HCV
- Highly sensitive in situ hybridization to detect viral genomes and mRNA levels of antiviral host genes in the HCV-infected livers
- Requires Fine Needle Aspiration of liver

Virologic and Host Markers and Endpoints

Current

Virologic Markers

- HBV DNA (q, non q)
- HBsAg (non q)
- HBsAg (q)
- HBeAg

Host Markers

- Anti-HBs (q/non q)
- Anti-HBc (q/non q)
- IgM and IgG
- Standard liver tests
- Imaging

Experimental

• *Virologic Markers*

- HBcrAg (q)
- cccDNA (q)
- Integrated DNA (q)
- HBV RNA

• *Host Markers*

- PD1, Tim3, CTLA4 expression (q) on HBV-specific CD8 T cells by Flow cytometry
- CD127 on HBV-specific T cells by Flow cytometry/ functional assays, Tregs
- Cytokines (q)
- HBsAg epitopes

HBsAg

- Two sources of HBsAg
 - cccDNA
 - integrated HBV DNA (the open reading frame of HBsAg S gene with its regulatory elements are usually still intact, not so for whole virions)
- Monitoring qHBsAg must take this into account
- qHBsAg may not truly reflect the amount of viral transcriptional activity in liver
- Are some inactive CHB really functionally cured? HBsAg only from integrated sequences
- Is there a way to distinguish the two sources?
 - Better assays

Government issues

- Low vaccine uptake in adults in US
- Still many CHB undiagnosed
- Many countries cannot provide long term therapy to patients with CHB
- Approve study of combination drugs early
- Risks may be highest in those with putative most benefit e.g. young
- Often side effects come out post registration

Emerging DAAs against HBV: Many currently in the pipe-line

- Entry inhibitors
- cccDNA inhibition or eradication
- siRNA-based strategies
- novel polymerase inhibitors
- capsid inhibitors/ modifiers
- Packaging inhibitors
- Secretion inhibitors
- Immune activators

Combination therapy will likely be required for cure

- Direct viral Inhibitors
- IFN, immune stimulant, TLR 7
- Checkpoint inhibitors PD-1/L1
- Therapeutic vaccine
- Adoptive T cell therapy

BUT

Emerging DAAs against HBV

Many currently in the pipe-line

BUT Selection of HBV patient will be critical

Optimization of HBV endpoints needed

DAAs may be enough for many

Immune modulators may lead to functional cure in some

Combination will likely benefit most patients