2017
LIFER:
update on phase II drug development

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Phase II trials: 2017 and beyond for HBV

Expanded Safety information

Narrow dose selection

Study therapy or therapies in expanded populations to determine efficacy

Establish correct path to phase III studies

Develop plans for combination therapies

HBV Phase II trial markers and goals

Oral > Sq > Infusions

3 to 12 months of therapy

1-3 log reduction of qHBsAg if monotherapy

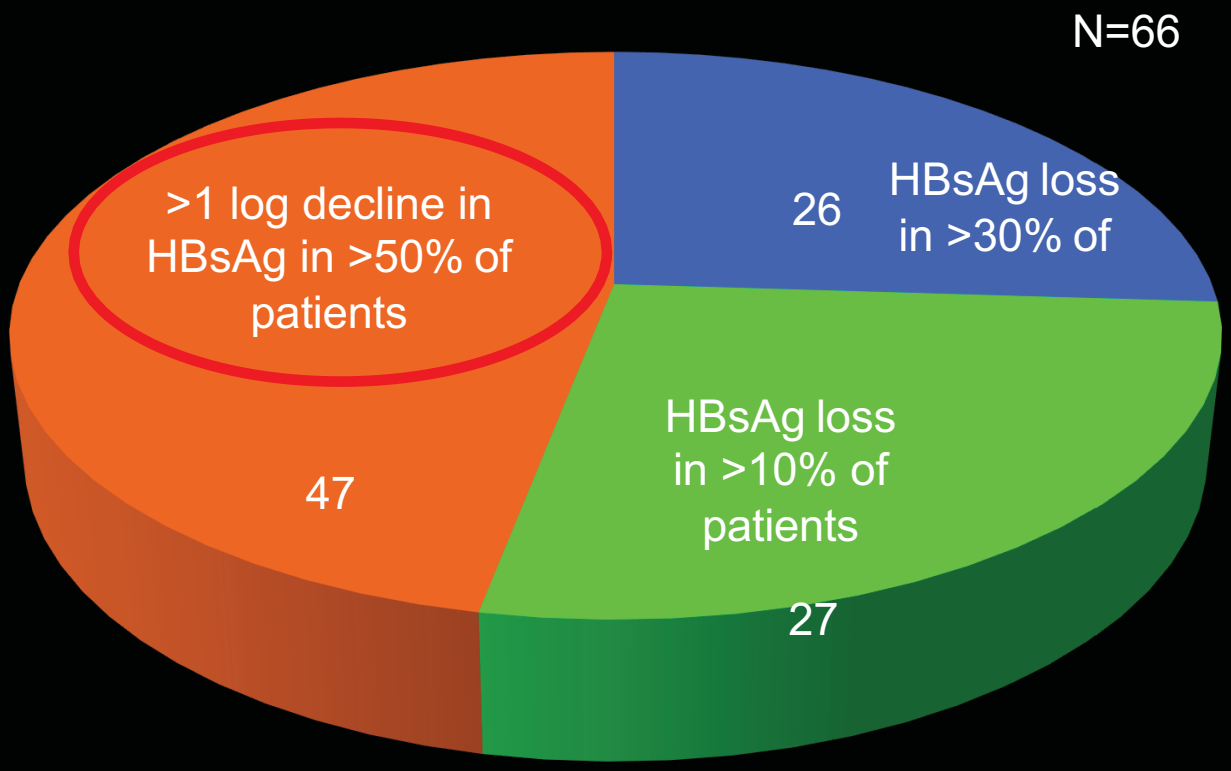
HBsAg clearance at 6-12 months of >20% if combination therapy

HBsAg clearance stable off therapy in > 90% of patients

HBcrAg, pgRNA, qJBV RNA, truncated q-mRNA from integrants, empty particles, cccDNA blood/FNA tissue, HBeAg quant if HBeAg(+), HBV DNA

Ref: Expert opinion R Gish

Survey Q: Effectiveness: Acceptable Definitions For Phase 2 Studies



AASLD/EASL HBV Treatment Endpoints Workshop Survey 2016

Key considerations

- Phase 2 or 3 studies
- Primary & secondary endpoints
- Antiviral vs. immunomodulatory drugs
- Treatment naive vs. virally suppressed patients
- Timing of endpoint assessment: on- or off-treatment
- Efficacy criteria for further development of drug

Biomarkers as surrogate endpoints

Biomarker

Characteristic that is objectively measured and evaluated as indicator of normal biologic processes, pathologic processes, or biological responses to therapeutic intervention

Surrogate endpoint

1. A validated substitute for clinical endpoint
2. Fully captures the net effect of treatment on the clinical outcome
3. Based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence

Prentice et al, StatMed 1989; Biomarkers Definitions Working Group, 2001

The ideal biomarker...

- Predictive (visible early, and indicative of, clinical outcome)
- High specificity
- High sensitivity, also correlation with severity
- Reflective of durable response
- High reproducibility
- Non-invasive/accessible
- Rapid/simple
- Inexpensive

Biomarkers Definitions Working Group, 2001

Clinical trial phases

20-100 volunteers

Phase 1a
Safety of single ascending dose

Phase 1b
Safety of multiple ascending doses

100-200 patients

Phase 2a
Optimal dose

Phase 2b
Efficacy prescribed dose

Pharmacokinetics & pharmacodynamics

500-2000 patients

Comparison to standard of care

Safety surveillance in 'real-life' patients

After H Janssen AASLD Virginia Meeting 2015

Current endpoints in HBV treatments

Biochemical:	ALT normalization
Virological:	HBV DNA decline/undetectability
Serological:	HBsAg/HBeAg loss/seroconversion
Histological:	Reduction of necrosis, inflammation, fibrosis
Combined:	Most often HBeAg, HBVDNA and ALT

Virological Markers to Follow CHB Patients

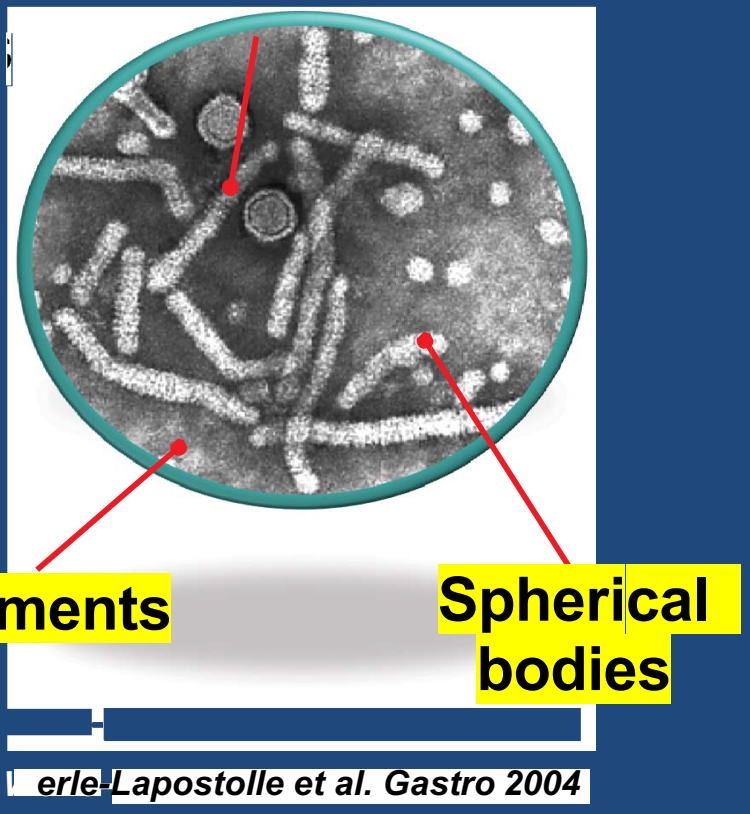
HBV DNA	Applicable to both HBeAg+ and HBeAg- Not really indicative of sustained immune control	Standardized assays available
Quantitative HBeAg	Applicable only in HBeAg+ More indicative of sustained immune control	Commercial assays not currently available
Quantitative HBsAg	Applicable to both HBeAg+ and HBeAg- Most indicative of sustained immune control	Standardized assays available

Immune control: HBeAg neg and low HBVDNA

After H Janssen AASLD Virginia Meeting 2015

Serum HBsAg Quantification

- HBsAg loss associated with better outcome
- Reflects number of infected hepatocytes and integrants
  - Association with transcriptionally active
    cccDNA level in HBeAg pos
    And integrants in HBeAg(-)
- Easily measured in serum
  - Produced in excess of virus particles
  - Standardized assays



erle-Lapostolle et al. Gastro 2004

Chan et al. Clin Gastro Hepatol 2007; Volz et al. Gastro 2007;

Defining HBV Cure

Functional cure

Associated with clinical benefit (disease progression and HCC)

Off-therapy sustained HBV suppression and disease remission

HBsAg serocnversion and cccDNA inactivation/reduction

Risk under immunosuppression

Feasible

Complete cure

Associated with clinical benefit (disease progression and HCC)

HBsAg seroconversion and cccDNA eradication

Feasibility uncertain

Removal of all integrants ?

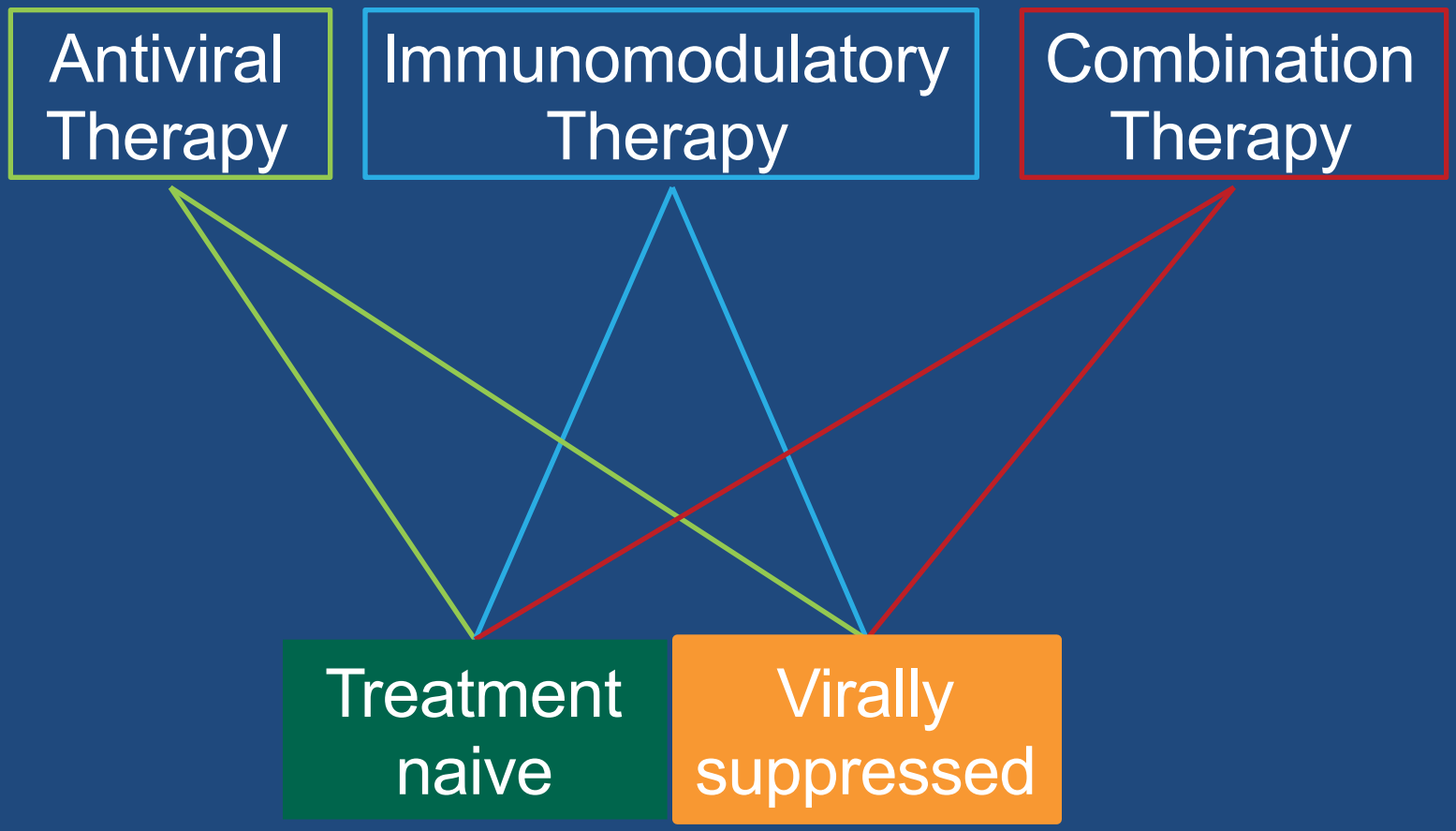
Zeisel, Lucifora et al, Gut 2015; Revill et al, Nature Reviews Gastroenterol Hepatol 2016

Survey: Surrogate for HBV cure (true/false)

Best endpoint for HBV cure	
HBsAg seroconversion	**61 (92.4%)**
HBsAg loss	43 (65.2%)
HBsAg decline	22 (33.3%)

Survey AASLD/EASL HBV Treatment Endpoints Workshop:
respondents n=66 about 45% academic, 45% industry, 10% rest group

Primary endpoint catered to treatment modality and patient group?



Experimental treatment in naive vs virally suppressed patients

Treatment Naive

Younger

Active Disease

HBVDNA can be used as a biomarker

No resistance

May be more likely to accept finite therapy

Suppressed

Have safe and effective therapy with reduction of HCC and improved survival

Partial immune restoration may benefit immune modifying therapy

Potentially better protection against flares

May have more objections to accept experimental therapy

Are HBeAg (+) and HBeAg(-) patients different

YES

All patients who have HBV DNA at baseline need to have core and precure mutations completed

HBeAg(-) patients have much more HBsAg that comes off of integrants1

HBeAg patients have lower qHBsAg, delta HBsAg may be truncated, thus need to follow absolute levels

mRNA from integrants may deliver HBsAg to serum even if cccDNA is gone/cleared

General safety monitoring for unexpected adverse events

- Regular monitoring + symptom directed assessment
- HBV: Flares of ALT and liver function such as bilirubin: balancing benefit and harm risk

- Non-specific inflammatory markers
- Organ specific toxicity
  - Renal: RFT, eGFR, (retinal-binding protein, beta 2 microglobulin)
  - Pancreas: amylase, lipase, glucose
  - Cardiac: CPK, ECG
  - Hematology: CBC, clotting profile
  - Lung: lung function test, CXR
  - Thyroid: STSH, FT3, FT4
  - Lipid metabolism: lipids
  - Muscle: CPK, clinical, (EMG, muscle biopsy)
  - Bone: bone profile, biomarkers of bone resorption and formation, (DEXA scan)
  - Neurology: clinical, (nerve conduction study)

Study 149: ALT Flare (Type 1) and Clinical Response to 48 Weeks of Tenofovir DF + PegIFN

- ALT flares occurred with tenofovir DF + pegIFN even with suppression of HBV DNA to undetectable levels
- ALT flares significantly associated with
  - HBsAg decline
  - HBsAg loss
  - HBeAg loss
- Magnitude of ALT flare
  - Impacts qHBsAg decline and HBsAg loss, but not HBeAg loss

Clinical Outcomes (Week 72)

	ALT Flare (n=29)	No ALT Flare (n=143)
HBsAg decline		
≥1 log10 copies/mL (%)	36*	12
HBeAg positive	28	11
HBeAg negative	46†	13
HBsAg loss (%)	24‡	2
HBeAg positive	28‡	2
HBeAg negative	18	2
HBeAg loss (%)	39§	11

*$P<0.005$; †$P<0.05$; ‡$P\leq0.0001$; §$P<0.01$.

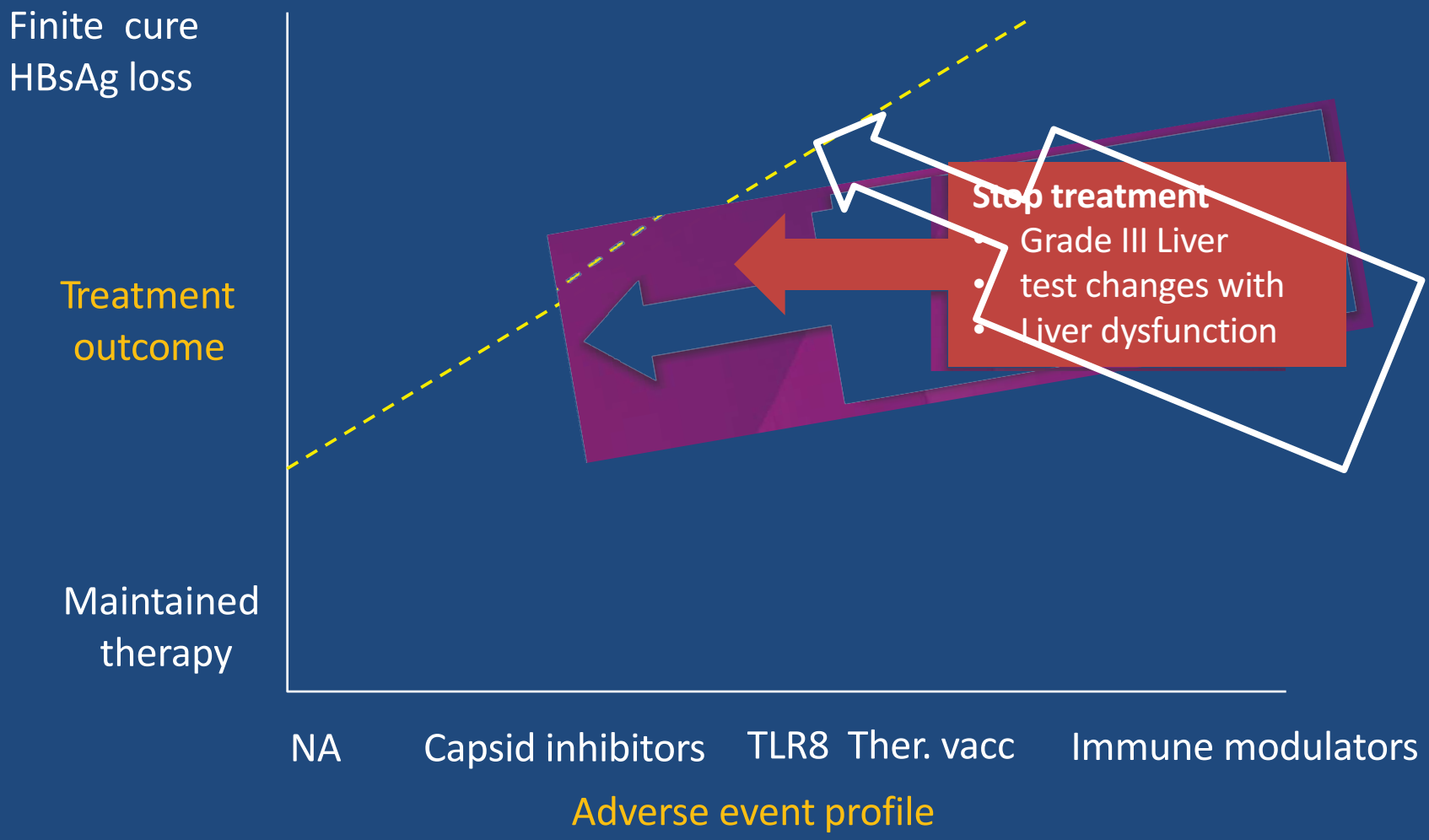
Chan HL, et al. *Hepatol Int.* 2016;10(suppl 1):266. Abstract P-0425.

Potential liver-specific adverse effects of novel antiviral agents

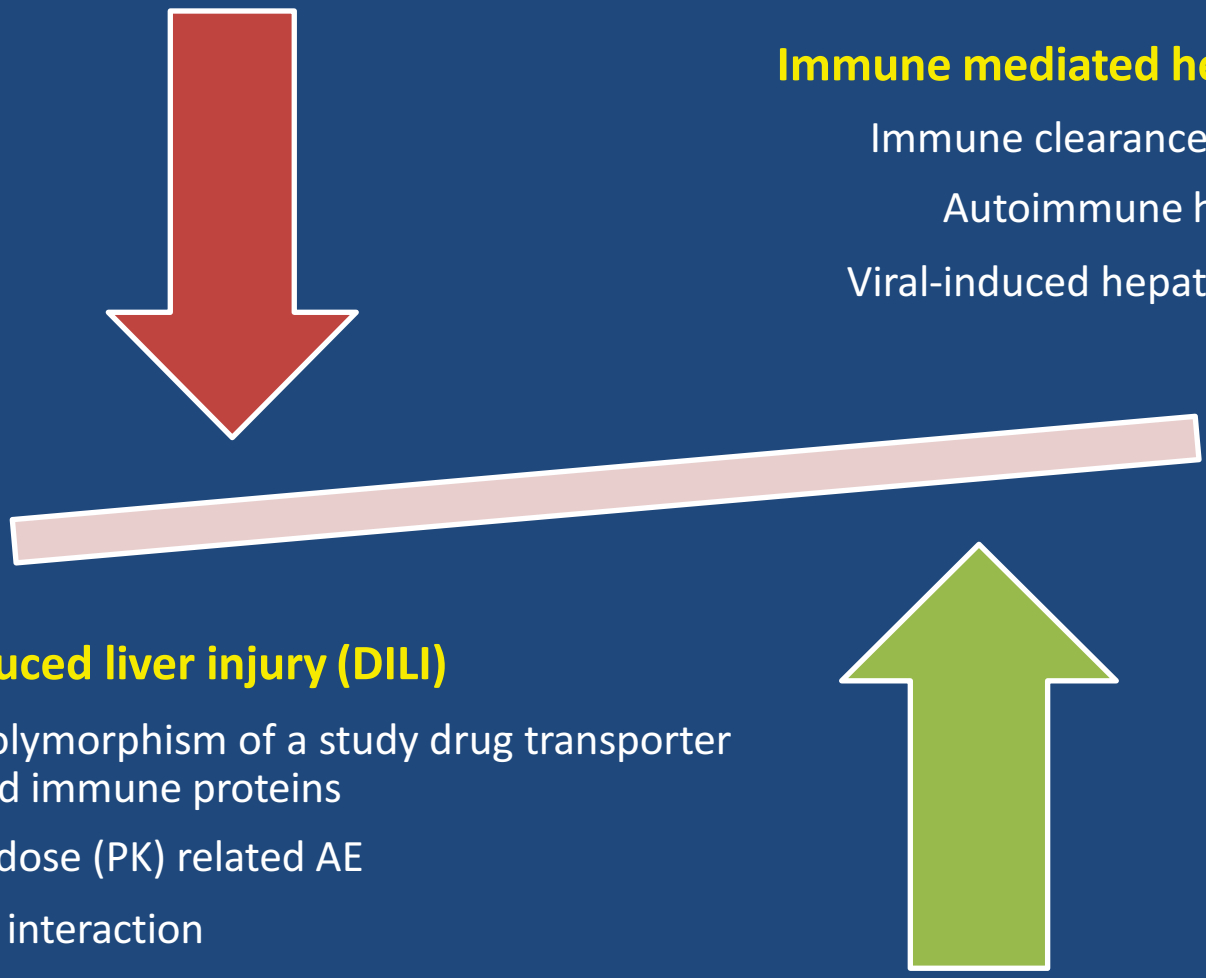
- Direct acting antiviral agents
  - Stimulation of immune system leading to on-treatment hepatitis flare
  - Hepatitis reactivation and flare after stopping treatment
  - Drug resistance
- Immunomodulatory agents
  - Hepatitis flares during and off treatment
  - Immune-related adverse events (hepatitis, skin rash, colitis, pancreatitis, nephritis, thyroiditis, adrenal insufficiency, diabetes)
  - Interferon-like adverse events

After Henry Chan Virginia AASLD HBV meeting 2016

How much adverse event can we tolerate?



HBV Liver safety considerations



Immune mediated hepatitis

Immune clearance of virus

Autoimmune hepatitis

Viral-induced hepatitis flare

Drug-induced liver injury (DILI)

Genetic polymorphism of a study drug transporter protein and immune proteins

Exposure/dose (PK) related AE

Drug-drug interaction

FDA recommendation on DILI management

- Identification by Hy's law
  - ALT > 3x ULN; and/or accompanied by increase in TBL to >2x ULN, with other potential etiologies excluded
- Confirmation and observation
  - Repeat testing within 48-72 hours with liver function assessment
  - If not subside, observe 2-3x weekly; then weekly or less if stabilized or trial drug is discontinued in asymptomatic patient
- Stop treatment
  - ALT/AST >8x ULN
  - ALT/AST >5x ULN for >2 weeks
  - ALT/AST >3x ULN and (TBL >2x ULN or INR >1.5)
  - ALT/AST >3x ULN and symptomatic (fatigue, nausea/vomiting, RUQ pain, fever, rash and/or eosinophilia)

FDA. Guideline for industry. Drug-induced liver liver injury: premarketing clinical evaluation 2009

Special considerations in HBV patients

- Elevated ALT at baseline due to the underlying disease, can be >3x ULN at baseline
- ALT elevation may be due to immune clearance of virus, which is desirable and transient
- Underlying liver cirrhosis may reduce the tolerability of ALT flare
- Off-treatment ALT flare is not DILI but may be related to viral reactivation
- DILI parameters should be modified to allow higher ALT and Bili if INR is normal

Further confusion on interpretation of ALT

- All previous recommendations of DILI monitoring based on laboratory ULN
  - varied among laboratories
  - usually at about 40 U/l

- AASLD recommended ALT ULN; used in clinical trials including inclusion criteria and outcome determination
  - Male 30 U/l
  - Female 19 U/l

Different ALT ULN used in patient recruitment and outcome measurement vs safety monitoring?

Terrault NA, et al. Hepatology 2016;63:261-83.

Recommendations and considerations for patients with pre-existing liver disease in a Boston workshop 2012

Workshop recommendation	Consideration
Patients with elevation of ALT/AST/ALP and increased serum direct bilirubin should be excluded (except Gilbert syndrome)	Avoid patients with severe underlying liver disease
Baseline liver tests stable over 2 time points approximately 1 month apart. Baseline ALT is computed as the mean value of a study subject's pre-treatment test results	Avoid patients with rising ALT or flare before treatment
Suspect worsening of liver injury if ALT increase to 2x above the nadir values during treatment; initiate confirmation and observation	Early detection of possible DILI in patients with pre-existing liver disease using INR

As modified from

Avigan MI, et al. Drug Saf 2014;37 Suppl 1:S19-31

Highest risk patients - underlying liver cirrhosis

- Patients with liver cirrhosis should be excluded from early phase studies
- Liver biopsy is not desirable
- Non-invasive assessment of liver fibrosis often used in clinical trial protocols
  - Fibroscan
  - Serum indexes

Considerations in management of liver adverse event

- Suspected immune-mediated flare
  - Continue study medication as far as possible, may reduce dose or interrupt treatment transiently
  - Perform liver biopsy at threshold
- Suspected autoimmune hepatitis
  - May need corticosteroid or immunosuppressive therapy (e.g. in anti-PD1 antibodies) and stop the study medication
  - Perform liver biopsy at threshold
- Suspected DILI
  - Reduce dose or stop study medication
  - Peform liver biopsy at threshold

Clues to differentiate flares?

	Immune mediated flare	Autoimmune hepatitis	DILI
Timing of flare	Usually within 24 weeks (interferon)	Can be very early with anti-PD1; 1-4 weeks [1]	Any time during treatment
Course of flare	Usually self-limiting within weeks	Fast and progressive, respond to steroid	Static or progressive
Association with HBV DNA	After HBV DNA decline	Unrelated	Unrelated
ALP level	Normal	Normal	Normal or elevated
Bilirubin	Usually normal	Normal or elevated	Can have cholestasis component
Liver biopsy	Not needed	May be needed for diagnosis	Can be non-specific

1. Hofmann L, et al. European J Cancer 2016;60:190-209

Proposed combined approach for stopping rule in HBV patients in a Boston workshop 2012

Proposed stopping rule for HBV patients with baseline ALT > ULN*

Baseline ALT value	Elevation during treatment
1 to less than 2x ULN	>5x from baseline and >10x ULN
2 to less than 5x ULN	>3x from baseline
Greater or equal to 5x ULN	>2x from baseline

*Consensus not reached in workshop

Kullak-Ublick GA, et al. Drug Saf 2014;37 Suppl 1:S57-062

Responsive Tests to work up flares

ANA, ANCA, ASMA, quant globulin panel, LKM, LC1, SLA

HEV IgM reflex to blood and stool PCR

Tox screen, blood alc, acetaminophen level

HCV antibody, HAV IgM

Additional comments

- Adequate pre-clinical assessment of drug metabolism and potential toxicity is needed to guide specific monitoring of safety in early phase clinical trials
- Need transporter interactions
- Consider SNP for immune related polymorphisms in ISG and others

- Careful patient selection to avoid high risk patients

- Need to revise the stopping rules and definition of DILI in chronic hepatitis B patients

- Need to define the duration of post-treatment follow-up and management of post-treatment ALT flares