FUTURE PROSPECTS
FOR THE TREATMENT OF HEPATITIS B

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Disclosure belangen spreker

Geen (potentiële) belangenverstrengeling
Hepatitis B

Limitations of current therapy

- All HBV nucleos(t)ides are generally well tolerated but with low rates of successful discontinuation: relapse 50-95% after stopping NA’s

- The long-term safety of nucleos(t)ide-analogues remains to be determined

- PEG-IFN monotherapy is finite but only effective in subgroup of patients and its use is limited due to toxicity
Hepatitis B

*Limitations of current therapy: Virus life cycle*
Hepatitis B

Limitations of current therapy: Virus life cycle


Serum HBV RNA? 1,2,3
Hepatitis B

Limitations of current therapy: Virus life cycle
Hepatitis B

New therapeutic approaches

1. Immune Modulators

IFN

Hepatocyte

cccDNA

Nucleus

Capsids

DNA

RNA

RT

SVP (HBsAg)

HBeAg

Virions?

Adapted from: Zoulim EASL 2015
Immune modulators

Overview

- Peg-IFN Lambda
- TLR agonists
- Therapeutic vaccination
- PD-1, PDL-1 blocking
**Immune modulators**

*Peg-IFN Lambda*  
*LIRA-B study*

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**Study Week**  
0  
24  
48  
72

- **Lambda**  
  180 μg weekly  
  Follow-up  
(N = 80)

- **Alfa**  
  180 μg weekly  
  Follow-up  
(N = 83)

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- **Key entry criteria:**
  - Adults with HBeAg+ CHB (HBsAg+ ≥ 6 months), HBeAb–, HBV DNA ≥ 10^5 c/mL
  - Interferon-naive, prior HBV nucleos(t)ide use allowed
  - ALT > upper limit of normal (ULN; 47 U/L) and < 10 × ULN
  - Cirrhotics (CTP class A; confirmed by liver biopsy/FibroTest): capped at 10%

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*Chan et al. EASL 2014*
Immune modulators

Peg-IFN Lambda  LIRA-B study

Week 48

Lambda 180 µg (N = 80)

14/80 (18%)
Seroreversion: – 4 patients
Other: – 3 patients
New seroconversion: + 4 patients

Alfa 180 µg (N = 83)

14/83 (17%)
Seroreversion: – 3 patients
Other: – 1 patient
New seroconversion: + 15 patients

Week 24 post-dosing

Lambda 180 µg (N = 80)

11/80 (14%)

Alfa 180 µg (N = 83)

25/83 (30%)

Chan et al. EASL 2014
Immune modulators

Overview

- Peg-IFN Lambda
- TLR agonists
- Therapeutic vaccination
- PD-1, PDL-1 blocking...early phases
Hepatitis B

New therapeutic approaches

1. Immune Modulators

IFN

Hepatocyte

2. Entry Inhibitors

Myrcludex B

3. cccDNA Targeting

4. Inhibition of Capsid Assembly

5. Polymerase Inhibitors

6. RNA Interference

SVP (HBsAg)

7. Targeting HBsAg (Production)

Adapted from: Zoulim EASL 2015
Entry inhibitor

*Myrcludex B*

- Chemically synthesized lipopeptides > envelope protein of HBV
- Prevents viral infection
Hepatitis B

New therapeutic approaches

1. Immune Modulators

2. Entry Inhibitors

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7. Targeting HBsAg (Production)

Adapted from: Zoulim EASL 2015
Inhibition of Capsid Assembly
EASL 2015 Klumpp et al: NVR 3-778

- Core inhibitor: NVR 3-778
- Induces the assembly of defective capsids

Abstract:
- 36 uPA/SCID mice infected with HBV
- Treated with NVR 3-778, entecavir, Peg-IFN, or combinations

Phase 1 trial:
- Ongoing..
Hepatitis B

New therapeutic approaches

1. Immune Modulators
2. Entry Inhibitors
3. cccDNA Targeting
4. Inhibition of Capsid Assembly
5. Polymerase Inhibitors
6. RNA Interference
7. Targeting HBsAg (Production)

Adapted from: Zoulim EASL 2015
Targeting HBsAg

EASL 2015: REP 2139-Ca

- Nucleic Acid Polymer: REP 2139-Ca
- Prevents subviral particle (SVP) formation

Phase II proof-of-concept trial (Dhaka, Bangladesh):
- REP 2139-Ca + immune modulator add-on

Al-Mahtab et al. Lancet Hepatitis Summit 2015
Conclusion

• New strategies to achieve true immune control?

• Inhibitors of the HBV life cycle are promising
  ..... but in early development

• Immune modifying agents combined with new antiviral agents?