Therapy of Hepatitis B

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Epidemiology

• about 40% of world population are anti-HBc positive
• 500,000 - 1.2 million deaths per year, number 10 cause of death worldwide
• 350 million HBV-chronically infected
  - 4 millions in West Europe
  - ca. 500,000 in Germany
Prevalence of chronic Hepatitis B-infection

HBsAg Prävalenz

- ≥8% – high
- 2%-7% – moderate
- <2% – low
Chronic Hepatitis B -infection: natural history

- Chronic infection: 23% in 5 years
- Cirrhosis: 30%
- Carcinoma (HCC): 5–10%
- Organ failure: death
- Acute flares

References:
Hepatitis B: therapeutic options

- **Vaccine**: prevention of infection
- **Early intervention with Lamivudine**: acute HBV infection: prevention of fulminant Hepatitis B
- **HBV-Polymerasehemmer (PEG)-IFN**: chronic Hepatitis B: prevention of cirrhosis
- **HBV-Polymerasehemmer (PEG)-IFN**: chronic Hepatitis B: prevention of HCC
Goals of antiviral therapy

<table>
<thead>
<tr>
<th>Lab values:</th>
<th>ALT↓ (normalization)</th>
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<tbody>
<tr>
<td>Virology:</td>
<td>durable HBeAg-Seroconv. (WT)</td>
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<tr>
<td></td>
<td>serum HBV-DNA↓ (&lt;10^4 cp/ml)</td>
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<td>Loss of HBs-AG</td>
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<tr>
<td>Histology:</td>
<td>Inflammation (Grading)↓</td>
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<td>Fibrosis (Staging) ↓</td>
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Diagnostic testing
# HBV- Infection

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<tr>
<th>HBsAg</th>
<th>anti-HBc</th>
<th>anti-HBs</th>
<th>HBV-DNA</th>
<th>HBeAg</th>
<th>anti-HBe</th>
<th>GPT</th>
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**Legend:**
- Norm
- +++
- +
- +/-
- -
- +/+norm

- Immuno-tolerance
- Hepatitis
- HBsAg-carrier-status
- Cure
### HBV- Infection

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<th>GPT</th>
<th>cirrhosis</th>
<th>HCC-risc</th>
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**“Hepatitis phase“ indication for antivirale therapy!**
When and how to treat?
Treatment in acute hepatitis B

- high spontaneous seroconversion in acute Hepatitis B in adults (95-99%)
- in a small randomized trial no positive effect for lamivudine in regard to HBs-Ag-seroconversion (92.5% with lamivudin vs. 97.5% with placebo at month 18) was detected
- in small series with fulminant hepatitis lower rate of ltx (20%) following lamivudine compared to historic controls (50-80%)

Kumar, Hepatology 2007; Tillmann, J. Viral Hep 2006
REVEAL-HBV-Study: Chen et al., JAMA Jan 2006
HCC-risk in pts. with normal liver enzymes

HBeAg(-) pts. with normal GPT, no cirrhosis (n=2,925)

Baseline HBV DNA Level (copies/mL)
- ≥10⁶
- 10⁵–<10⁶
- 10⁴–<10⁵
- 300–<10⁴
- <300

viremia > 10⁴ copies/ ml (2 x 10³ IU/ ml) cutoff for risk of HCC
Hepatitis without cirrhosis

*Elevated* GPT (>2xNorm) and viremia > $10^4$ copies/ml ($2 \times 10^3$ IU/ml)

New: no difference whether HBe-Ag positive or negative

=> treat
What if?

**normal** GPT (<2xNorm) and viremia > $10^4$ copies/ml (2 x $10^3$ IU/ml)

$\Rightarrow$ biopsy

- with inflammation or significant fibrosis (>F1)
  - treat

- no inflammation or significant fibrosis (≤F1)
  - wait and watch: GPT/ GOT and HBV-DNA every 3-6 months
How to treat?
Antiviral drugs

- Telbivudin (licensed in 2005/6)
- Entecavir (licensed until 2004)
- Lamivudin (licensed in 2005/6)
- Interferon-alpha (licensed until 2004)
- Adefovir (licensed in 2005/6)
- PEG-IFNα-2a (licensed until 2004)
- Tenofovir (licensed in 2005/6)
- Clevudin (Phase II/III-Studies)
- Pradefovir (Phase II/III-Studies)
- Telbivudin (Phase II/III-Studies)
- Pradefovir (Phase II/III-Studies)

active against HBV, licensed only for HIV
in some countries licensed
**IFN vs. Polymerase-Inhibitors**

**(PEG)-INTERFERON ALPHA**

- HBs-seroconversion up to 10%
- HBe-seroconversion up to 50% in HBV-Genotype A
- no resistance (?)
- defined treatment duration

- adverse effects, contraindications (e.g. advanced cirrhosis)
- low effectivity with high HBV-DNA and low activity (ALT)

**HBV-Polymeraseinhibitors (nucleos(t)ide-analogues)**

- high antiviral potency
- few adverse effects
- no constraints in patients with advanced cirrhosis

- development of resistance
- relapse with stopping drug
- long term therapy may be necessary
Interferon
HBV - genotypes
HBV Genotypes

spontaneous HBeAg seroconversion

with genotype B earlier and more frequent than with C

inflammation and progression to cirrhosis

C > B (?), D > A
PEG-IFNa-2b +/- Lamivudin: Loss of HBeAg by genotype

Janssen et al, Lancet 2005
HBsAg-seroconversion by genotype

Peginterferon alfa-2a

p<0.0008

Tillmann HL et al. WJGastro 2007;7:125ff
What influences response to Interferon-a?

• HBV-genotype A
  - >20% HBsAg-seroconversion
• low viral load (<10^6 copies/ml)
• ALT/AST at least 2xULN (even better 5x)
• not pretreated
Contraindications for Interferon

- pregnancy, lactation period
- severe psychiatric comorbidity
- GPT (ALT) >10xULN
  - risk of acute flare
- advanced cirrhosis (Child B+C)
- thrombocytopenia (<50.000/µl), leukopenia (<2.000/µl)
- autoimmune disease
Standard-IFN versus PEG-IFN?

- Interferon alfa-2a (Roferon®)
  ➢ (2.5-5 Mio. I.E./m² 3x/week)
- Interferon alfa-2b (Intron A®)
  ➢ (5-10 Mio. I.E. 3x/week)
- Pegylated Interferon alfa-2a (Pegasys®)
  ➢ (180µg/Woche s.c. for 48 weeks)

PEG-Interferon is generally preferable, noninferior in effectivity but more convenient (only 1x/week)
Nukleos(t)ide-analogues
Nucleos(t)id analogues - problems

Lamivudin (Zeffix®)

"It is easy to start but, difficult to stop"

Dienstag et al. NEJM 1999

J. Hofnagle personal note
Lamivudine (Zeffix, Epivir-HB, Epivir)

- Cytidine nucleoside analogue, initially developed for treatment of HIV-infection
- dose in HIV-infection 300mg/d, in Hepatitis B-infection 100mg/d
- high safety, low rates of adverse events resistance can rapidly emerge
Adefovir (Hepsera)

- adenine-nucleotide analogue, initially developed for HIV-infection
- doses evaluated in HIV-infection 60 and 120mg/d, nephrotoxic
- in Hepatitis B dose of 10mg daily effective
- lower rate of resistance development than lamivudine, primary resistance
Entecavir (Baraclude®)

Guanosin-Nukleosidanaloge
  -> very high antiviral potency

• Ideal for pts. with
  – high HBV-DNA
  – cirrhosis

• development of resistance
  – in pts without previous Lamivudin: <1% in 3 years
  – can develop cross resistance to lamivudine in HIV-infection?
Tenofovir (Viread)

- adenine- nucleotide analogue
- developed and licensed for HIV-infection
- low rate of resistance development
- second line drug
- dose 245 mg/d
Telbivudine (Tyzeka, Sebivo)

- Thymidine-Analogue, dose 600mg/d
- in randomized studies over 48 weeks superior to Adefovir in viral suppression
- cross resistance with lamivudine possible
HBV DNA Suppression within one year in nucleoside-naïve patients*

* = no direct comparison

HBeAg(+)  

HBeAg(-)

* Non detectable <300 Kopien/mL  
# Non detectable <400 Kopien/mL  
§ Non detectable <1000 Kopien/mL

Nukleos(t)ide-analogues: Duration

HBeAg+
- Seroconversion HBsAg-/anti-HBe+
  - After seroconversion 6-12 months

HBeAg-
- No seroconversion
  - Continue

Stop therapy with HBsAg-Seroconversion with anti-HBs>100 IU/l
Development of resistance
How to react?
Resistance: Definition

**Primary resistance**
- with no drop in HBV-DNA by at least 1 log in 3 months

**Secondary resistance**
- with a rise in HBV-DNA by at least 1 log on therapy
Development of resistance

- Lamivudin\(^1\)
- Adefovir\(^2,3\)

*HBeAg(+) und HBeAg(-) Patienten

1. Lok et al. *Gastroenterology* 2003;
2. Qi et al. *J Hepatol* 2004;
3. Locarnini et al. EASL 2005
# K. Borroto-Esoda, DDW 2006.
Patterns of Resistance

Mutations seen in viral breakthrough

Lamivudin

Telbivudin

Adefovir

Entecavir

How to react to resistance to Lamivudine?

“Add on” or “switch”? 

Lamivudin

Nukleotid (Adefovir)

Lamivudin

Nukleotid (Adefovir)

Lamivudin

Nukleosid (Entecavir)
Risk of Lamivudine-Resistance higher with more viral replication

Serum HBV-DNA Level after 6 months (copies/mL)

- < 200 (n = 12): 8%
- < 10^3 (n = 23): 13%
- < 10^4 (n = 41): 32%
- > 10^4 (n = 118): 64%

*with high viremia: no lamivudine monotherapy*

*Median follow-up: 29.6 months.*

Entecavir in Lamivudin-Resistance

Lamivudin n=145
Entecavir n=141

But: in patients with lamivudin resistance:
Entecavir-resistance 25% in 3 years

Naive HBe-Ag positive pts: -6.9 log
LAM-R HBe-Ag positive pts: -5.1 log

Sherman M. et al., Gastroenterology 2006;130: 2039-2049
How to react to Adefovir-Resistance?

- **no lamivudin-pretreatment:**
  - Entecavir
  - Lamivudin („add on“)
  - Tenofovir (only licensed for HIV)
  - Telbivudin (limited to some countries)

- **lamivudin-pretreatment:**
  - Tenofovir (only licensed for HIV)
Adefovir-resistance in pts treated with Adefovir + Lamivudin*

*Based on experience in controlled clinical trials.
†2 patients enrolled in Study 435, initially on combination therapy with ADV + LAM, and subsequently selected ADV resistant mutation N236T. However, they were on ADV monotherapy when ADV resistance mutation was detected.

Tenofovir in pts with incomplete response to Adefovir

19/20 Patienten with HBV DNA < 400 cop/ml nach 4 (1-8) Monaten

How to react to Entecavir-resistance?

- treat with Nukleotid-analogue
  - Adefovir
  - or Tenofovir
Combination therapy: (PEG)-Interferon plus Nukleos(t)ideanalogue?

=> Currently not recommended
Prophylactic Therapy
Prophylaxis with high dose chemotherapy or immunesuppression

rate of reactivation in HBsAg-pos. pts.: 15-50%

• HBsAg-+ Pts
  - treat prophylactically
    high viremia: Entecavir or Lamivudin+Adefovir
    low or negative viremia: Lamivudin
  - continue for at least 3-6 Mon. after chemotherapy

• Anti-HBc-, HBsAg-neg. pts:
  - watch closely
  - antivirale therapy with rise of HBV-DNA or development of HBs-AG
Therapy in Pts. with Cirrhosis?
Cirrhosis and chron. Hepatitis B

With positive viremia

=> treat always
Lamivudin in pts. with HBV-assoc. cirrhosis: organ failure and HCC

progression to organ failure or hcc

Placebo (n=215)
Lamivudin (n=436)

P=0.001

Liaw NEJM 2004
Lamivudin in pts with HBV-assoc. cirrhosis: YMDD-Mutation

Liaw NEJM 2004
Therapy of Hepatitis B with Cirrhosis

Cirrhosis

measurable viremia

HBV DNA ≥ 10^4 Kopien/mL

(PEG-)IFN (only CHILD A)

or

Entecavir

or

combination therapy, eg. Lamivudin plus Adefovir

no cutoff in ALT

HBV DNA < 10^4 copies/mL

(PEG-)IFN (only Child A)

or

Nukleos(t)idanalogue

HBV DNA ≥ 10^5 Kopien/mL

HBV DNA < 10^5 copies/mL

measurable viremia
Conclusions I

**pts. without cirrhosis:**
- elevated GPT/AST (>2x ULN) and viremia > $10^4$ copies/ml
  - treat
- normal GPT/AST (<2x ULN) and viremia > $10^4$ copies/ml
  - biopsy
  - with inflammation or fibrosis > F1 => treat

**pts with advanced fibrosis or cirrhosis:**
- with positive viremia
  - treat

**pts. with high-dose chemotherapy or immune suppression:**
- HBsAg-positive pts
  - treat prophylactically (at least until 3-6 Mon. after chemotherapy)
**PEG-IFNa-2a:** Jyounger patients; GPT >ULN; low viral load (<10⁶ copies/ml); genotype A; duration (6-)12 months

**Lamivudin:** long term safety - problem development of resistance  
- in resistance: add on adefovir  
- cave: cross-resistance with Telbivudin, Entecavir (partial), Tenofovir

**Adefovir:** add-on in lamivudine resistance, combination with lamivudin in selected patients

**Tenofovir:** with primary or secondary resistance to Adefovir, not yet licensed for HBF

**Entecavir:** preferred in Lam-naiven pts. with advanced fibrosis/cirrhosis  
with high viral load  
higher dose (1 mg statt 0,5 mg) in Lam-resistant pts.

**Telbivudin:** licensed only in some countries