Grand Rounds
Treatment of hepatitis B

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December 20, 2007

objectives

- Who to treat
- how to treat
- Prevention of reactivation

Hepatitis B patient1

- 35 year old Asian male presents to clinic 11/03 with known chronic hepatitis B. He reports that he failed lamivudine therapy and has been on tenofovir x 1 year with no response
- PMHx Depression and hypertriglyceridemia
- Meds: tenofovir, lithium, and desipramine
- PE: normal
- Labs ALT 58, HBsAg pos

Hepatitis B patient1

July 2004

- HBeAg positive, HBeAb negative
- HBV viral load >10 million copies/ml
- U/S echotexture suggestive of fatty liver

Hepatitis B patient1

January 2005

- Liver biopsy: chronic hepatitis with mild inflammatory activity, mild periportal fibrosis and marked macrovesicular steatosis. Positive immunoreactivity HBs and HBc

Hepatitis B patient1

October 2006

- Mild RUQ pain for 8 months
- ALT 496, AST 412, bili 1.3, Alk phos 117
- Started on peginterferon

Hepatitis B patient1

January 2007

- ALT 244, AST 112, bili 1.3, Alk phos 380
- HBeAg +, HBeAb -
- HBV DNA 552,000

Hepatitis B patient1

November 2007

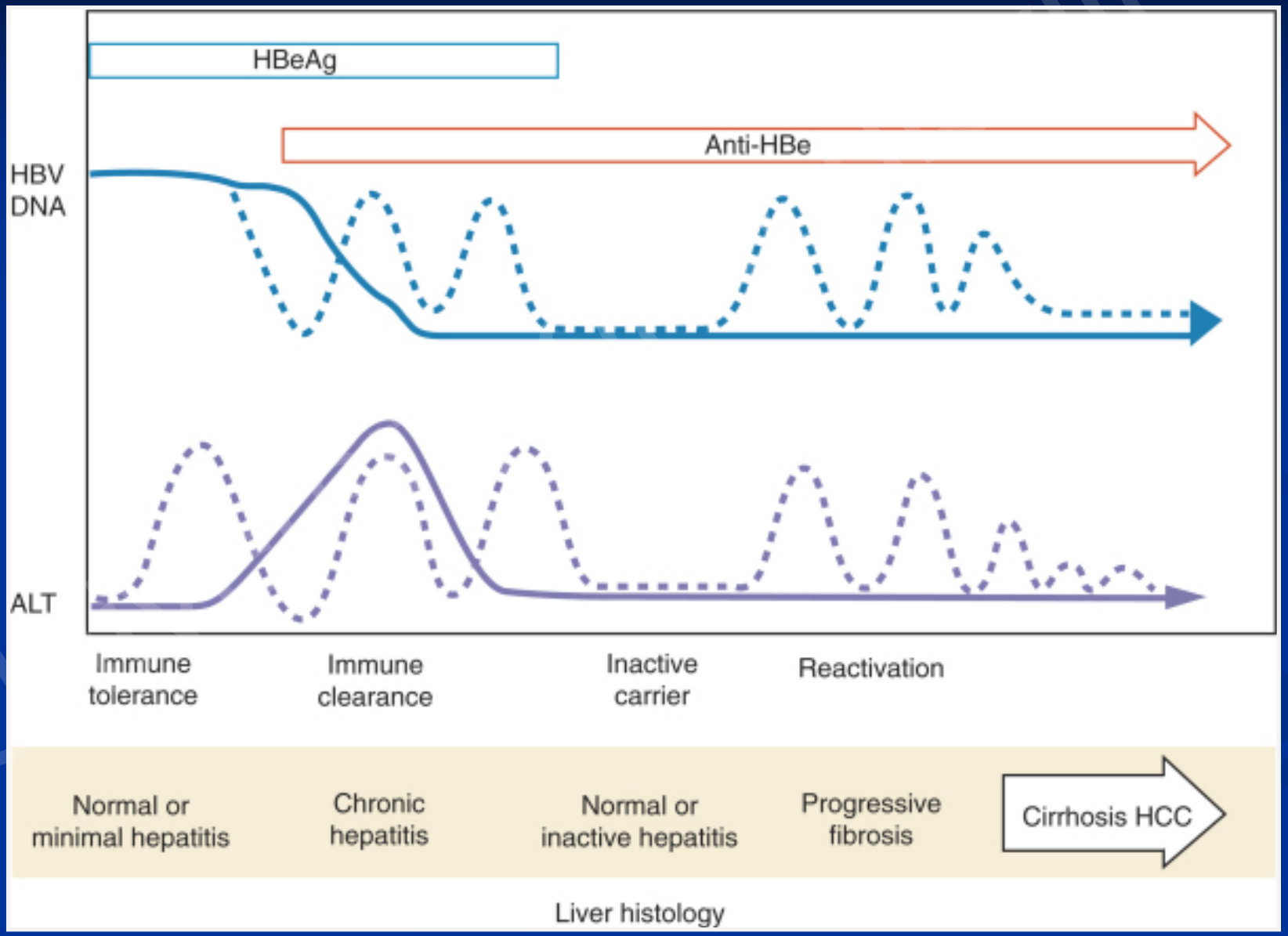
3 weeks following last dose of peginteferon

- ALT 24, AST 44, bili 0.6, Alk phos 93
- HBeAg +, HBeAb -
- HBV DNA 700

Hepatitis B patient

- Role of liver biopsy in workup of HBV pt
- Which medication to choose
- Endpoints of therapy

Natural history of hepatitis B



4 phases

- Immune tolerant
- Immune clearance
- Inactive carrier state
- reactivation

4 phases

- Immune tolerant
  - HBeAg +
  - Persistantly normal ALT
  - High HBV DNA (>10^5 copies/ml)
  - Liver biopsy: minimal changes
- Immune clearance
- Inactive carrier state
- reactivation

4 phases

- Immune tolerant
- Immune clearance: immune response to HBV, hepatocyte damage, occasionally hepatic decompensation
  - HBeAg +
  - High HBV DNA(>10^5 copies/ml)
  - Elevated ALT
  - chronic hepatitis on liver biopsy
- Inactive carrier state
- reactivation

4 phases

- Immune tolerant
- Immune clearance
- Inactive carrier state (70-85% of HBeAg-)
  - HBeAg -, HBeAb +
  - HBV < 10^4 copies/ml (2000 IU/ml)
  - Persistantly normal ALT/AST
  - No inflammation on liver biopsy
- reactivation

4 phases

- Immune tolerant
- Immune clearance
- Inactive carrier state
- Reactivation (rate 1.5% per year, 20% of carrier state pts)
  - With or without HBeAg seroconversion
  - May be spontaneous or be caused by immunosuppression

Precore mutants

- Core gene codes for HbcAg and HBeAg
- Core antigen is a protein in the nucleocapsid and is required for viral replication
- Loss of HBeAg (15-30% of HBeAg -)
- increased HBV DNA titers > 20,000 IU/ml
- HBV DNA 2000-20,000 IU/ml may be wild type or precore mutant
- Persistantly elevated ALT or fluctuating ALT
- Associated with more severe liver disease

Resolved hepatitis B infection

- Previous history of hepatitis B
- Clearance of HBsAg: occurs at rate of 1.5% per year in inactive carrier state
- Associated with better prognosis than HBsAg positive state

Risk factors for progression

- Older age
- High levels of HBV DNA
- Recurrent acute flares
- Genotype C
- Alcohol
- Smoking
- Coinfection hepatitis C, HIV
- diabetes
- Histological staging

Who to treat ? HBV

- HBV DNA levels correlate with prognosis
- Titer correlates with HCC risk
- Incidence of cirrhosis (n=3582, followed for a mean 11 years)
  - 5 % for viral load < 300 copies/ml
  - 36% for viral load > 10^6 copies/ml

Who to treat ? HBV

- Diagnostic threshold for chronic hepatitis has been set at 10^5 copies/ml
- HBeAg - hepatitis HBV DNA titers fluctuate widely, so serial monitoring is required
- HCC and cirrhosis can occur in patients with lower HBV DNA titers

Who to treat? ALT

- Korean population based study indicate a greater chance of liver related mortality with ALT > 20 for females and 30 for males => ULN 19 IU/L for women and 30 IU/L for men

Who to treat? Significance of HBeAg+ vs HBeAg - chronic hepatitis

HBeAg +

- Spontaneous seroconversion of HBeAg + to inactive carrier state can occur (10% per year in western patients).
- Slower rate of progression
- Easier to treat

HBeAg -

- Spontaneous remission is rare without treatment
- More rapid progression
- More difficult to treat
- eAg loss cannot be used as goal of therapy, more difficult to define duration of treatment

Who to treat?

- HBeAg positive and HBeAg negative with HBV DNA >20,000 IU/ml (100,000 copies/ml) and ALT > 2xULN

- If lower HBV DNA or ALT, or age > 35, consider liver biopsy and treat if active or advanced liver disease
- Cirrhosis
  - Compensated and HBV DNA > 2000 IU/ml
  - Decompensated and detectable HBV DNA

Goals of treatment

- Prevent HCC and cirrhosis
- Convert to inactive carrier state
- Viral suppression
- Normalization of ALT
- Loss of eAg
- Improvement in liver histology
- Loss of sAg

Treatment for hepatitis B

- Interferon: Peg interferon alfa-2a
- Nucleoside and nucleotide analogs
  - Lamivudine
  - Adefovir
  - Entecavir
  - telbivudine

Hepatitis B case

- In patients with chronic hepatitis B, interferon therapy is best suited for which of the following groups of patients
  - Patients with compensated disease, a low ALT level and high HBV level
  - Patients with compensated disease, a high ALT level, and a low HBV DNA level
  - Patients with compensated disease and evidence of cytopenia
  - Patients with decompensated disease, a low ALT level and a high HBV level
  - Patients with decompensated disease, a high ALT level and a low HBV DNA level

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Interferon and hepatitis B

- Advantages:
  - Finite duration of treatment
  - Does not select for resistant mutants
  - HBsAg loss occurs in 5-8% of treated patients, and 11-25% after 5 years of followup.

Interferon and hepatitis B

- Disadvantages
  - Can cause flares of hepatitis which can lead to hepatic decompensation
  - Cannot be used in decompensated liver disease
  - Side effect profile

Predictors of response for interferon

- Elevated ALT, Low HBV DNA (more common in western pts than pts who acquire HBV at young age)
- HBeAg positive more likely to have sustained response than HBeAg negative

Predictors of response for interferon

- PegINF vs lamividine trial in HBeAg +: seroconversion in 27 % of patients at end of 48 weeks of tx, 32% seroconversion 24 weeks later
- PegINF vs lamividine trial in HBeAg -: sustained response (normal ALT and HBV DNA undetectable by PCR) 15% 24 weeks after 48 weeks of treatment
- *Meta-analysis: loss of HBsAg occurred in 71% of over 6 year followup sustained responders*
- HBeAg - pts with sustained response 20% cleared HBsAg at 5 years

Predictors of response for interferon

- Therefore when considering interferon, think about
  - HBV titer, ALT
  - HBeAg status
  - Comorbidities
  - Cirrhosis? Compensated?

Nucleoside analogs

- Replace natural nucleosides during synthesis of HBV DNA
- Partially and reversibly suppress viral replication
- Advantages
  - Less side effects and less expensive than interferon
- Disadvantages
  - Need to be given for more than 1 year
  - HBsAg clearance is rare
  - Resistance can occur: can cause severe liver disease, reversal of histologic improvements

Outcomes of therapy

- Early response to antiviral therapy with oral nucleosides and nucleotides is predictive of treatment outcomes
- Duration of therapy
  - For HBeAg + treat for 6 months after seroconversion of HBeAg
  - For HBeAb - treat indefinitely

Comparing medications

- Resistance rates
  - Lamivudine (65-70% at 5 years)
  - Telbivudine (21.6% in HBeAg + and 8.6% in HBeAg - at 2 years)
  - Adefovir (29% at 5 years)
  - Entecavir (1% at 4 years but 39% at 4 years in lamivudine resistant patients)
- Viral suppression
  - Entecavir and telbivudine >
  - Lamivudine >
  - adefovir

Lamividine

- Advantages:
  - Low cost
  - At 5 years, 50% of pts seroconvert (loose eAg), 70% normalize ALT and have improved histology
- Disadvantages
  - High rate of drug resistance

Lamividine

- Therefore use if treatment duration is expected to be short
- Avoid in cirrhotics because flareup associated with resistance may be poorly tolerated
- Avoid in HBeAg - pts as they will need long term therapy

Adefovir

- Good response in both HBeAg + and HBeAg - pts
  - HBeAg + study: 72 weeks - undetectable HBV DNA 50%, normal ALT 75%, HBeAg loss 44%
  - HBeAg - study: 5 years - undetectable HBV DNA 67% and normal ALT 70%
- Safe in decompensated cirrhotics
- useful in lamivudine resistance
- nephrotoxicity

Entecavir

- Also good response rates in HBeAg+ and HBeAg - patients
- Can be used for lamivudine resistant patients

Telbivudine

- Selects for the same resistant mutants as lamivudine
- Slightly more potent than lamivudine and adefovir

Hepatitis B case

- A 31 year old caucasian male presents to you with a history of HBeAg positive hepatitis B infection. Two years ago he was treated with Peg interferon alpha2a 180 mcg weekly for 6 months. He was recently diagnosed with non Hodgkins lymphoma and will begin chemotherapy in the next several weeks. He has now been referred to you for further management
- Current hepatitis B status
  - HBeAg negative, HBeAb positive
  - HBsAg positive, HBsAb negative
  - HBV DNA undetectable
  - ALT/AST less than 30 U/L

Hepatitis B case

- The best current management for this patient's hepatitis infection is
  - Close monitoring of hepatitis B status while patient is receiving chemotherapy
  - No change in overall management plan, as this patient has cleared the virus and does not require further GI input
  - Peginterferon therapy while undergoing chemotherapy
  - Oral antiviral therapy during and for 6 months following his course of chemotherapy

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Hepatitis B reactivation

- Spontaneously 3% per year
- With immunosuppressive therapy 20-50% per year.
- Virus escapes immune control and replicates in hepatocytes. When host immune response is restored, HBV infected cells are destroyed.
- Greater risk if
  - HBeAg pos or HBV DNA > 10,000 copies/ml
  - Male
  - Chemotherapy involving corticosteroids
- Can occur even in HBsAb and HBcAb positive patients
  - HBV DNA may persist in liver tissue and peripheral mononuclear cells

Hepatitis B flare: labs

- ALT > 5x ULN or > 3x baseline level
- HBV lags behind transaminases, may be low or undetectable HBV DNA levels
- Increased HBcAB IGM

Hepatitis B reactivation

- Chemotherapy
- Transplantation especially stem cell transplantation
- Anti - TNF therapy
- Corticosteroid therapy
- HIV
- Superinfection with other hepatitis viruses

Hepatitis B reactivation

- Lamivudine, start at least 1 week before chemotherapy and for 6 months following chemotherapy
- Reactivation following stopping lamivudine more likely if HBeAg+, prechemotherapy HBV > 10^4 copies/ml (2000 IU/ml)
- Continue treatment with same endpoints as immunocompetent patients

Prevention of hepatitis B reactivation

- Controlled studies done with lamivudine
  - Case control, cancer chemotherapy, N=65, HBsAg +, 11%HBeAg+, reactivation 5 vs 25%
  - RCT, lymphoma chemotherapy, N=30, HBsAG +, reactivation 0 vs 53%
  - RCT, HCC, chronic HBV infection, transarterial chemo, reactivation 30 vs 5%
- Adefovir or entecavir reasonable alternatives if > 12 months therapy anticipated (AASLD guidelines)

Anti TNF agents

- Case series
- N = 80 Crohn's patients, treated with infliximab, 3 pts HBsAg positive.
  - One patient was treated with lamivudine, no problems
  - 2 patients not treated with lamivudine had reactivation when infliximab was withdrawn, 1 pt died.

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