Hepatitis in immunocompromised hosts

Cristina Valente
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Hepatitis in immunocompromised hosts

• Hepatotropic virus infections are common in immunocompromised hosts
• Physiopathological mechanisms are not well known
• Several mechanisms (i.e. humoral and cellular) play a vital role in the elimination of these viruses
Hepatitis in immunocompromised hosts

• Important questions
  – Are clinical and biological aspects of acute viral hepatitis modified by immunosuppression?
  – Is the risk of progression to chronicity and severity of hepatic disease influenced by immunosuppression?
  – Are both prophylaxis and treatment of viral hepatitis modified in the presence of immunosuppression?
Hepatitis in immunocompromised hosts

• Facts
  – Immunosuppression itself doesn’t increase the prevalence of fulminant hepatitis (i.e. HBV), but the risk of reactivation is high
  – Risk of chronicity is high in the presence of immunosuppression, independently of its aetiology, but it increases based on the degree of the immunological compromise (i.e. HIV +)
  – In dialysis patients the risk of progression is 40-80% (vs 2-5%) in HBV and 85-95% (vs 70-80%) in HCV
Hepatitis in immunocompromised hosts

1. Hemato-oncologic patients
2. Haemodialysis patients and renal allograft recipients
3. Liver transplant recipients
4. HIV positive patients
1. Hemato-oncologic patients

- Viral reactivation in hepatitis B surface antigen (HBsAg carriers) is now a well-recognized complication in patients who undergo immunosuppressive therapy (i.e. chemotherapy or corticosteroids).
- This condition ranges from asymptomatic self-limiting anicteric hepatitis to severe, potentially fatal progressive decompensated hepatitis (i.e. lymphomas).
- Mortality rates due to reactivation -5-37%
1. Hemato-oncologic patients

- HBV reactivation ranges from 14-50%* and has been reported in over 50% of the patients in settings of hematopoietic stem cell transplantation**, associated with 5-12% mortality.
- Reactivation of HBV can occur in:
  - haematological malignancies
  - other carcinomas
  - non-malignant conditions (i.e. cryoglobulinemia, vasculitis, malignant histiocytosis or ulcerative colitis)

*Blood 2002; 100 (2): 391-96
**Hepatology 2006; 43(2): 209-20
Mechanisms of HBV reactivation

- Enhancement of viral replication leading to an increase of infected hepatocytes, is due to 2 possible mechanisms*/**:
  - After withdrawal of the immunosuppressive agent and restoration of immunocompetence, activated T cells may attack the infected hepatocytes, leading to their rapid destruction.
  - The hepatic injury could be a direct cytopathic effect of HBV as a result of accelerated viral replication, leading to hepatocyte lysis.

* Blood 1999; 93: 1127-36
** Blood 2002; 100 (2): 391-96
HBV reactivation

- **Definition**: increase of HBV DNA levels of 10-fold or greater compared with the baseline level or an absolute increased level that exceed > 9 log (cp/mL) during or after chemotherapy in the absence of other infections.

* Hepatology 2006; 43(2): 209-20
Groups with prior HBV exposure are at risk for reactivation

- **Chronic infection**: patients who develop increases in serum HBV DNA and disease activity during chemotherapy
- **Inactive carriers**: patients who are HBsAg positive and HBV DNA negative and convert to active replication during chemotherapy
- **Immune or Viral Clearance**: pt with immunity against HBV due to past exposure (HBsAg neg, anti-HBs + and anti-HBsAc+) who reactivate with production of HBsAg and HBV DNA (risk of seroreversion)
Risk factors associated of high risk of HBV reactivation*

- Young age
- Male sex
- Lymphoma
- HBeAg+ (?)
- Pre-chemotherapy HBV viral load/ ALT (?)
- cccDNA
- Doses of chemotherapy
- steroids

* Br J Cancer 2004; 90: 1306-11
Prevention of HBV reactivation

• All candidates for chemotherapy and immunosuppressive therapy should be screened for HBsAg and anti-HBc antibodies prior to initiation of treatment

• Vaccination against HBV in seronegative patients is highly recommended*

* J Hepatology 2009; 50: 227-42
Prevention of HBV reactivation

In all HBsAg+
- check viral load (HBV DNA)
- start antiviral therapy regardless of HBV DNA status* (preferably within 2-4 w before treatment)
- follow-up of ALT, HBV DNA
- consider discontinuation of antiviral agent at 6-12 months after cessation of chemotherapy**

* J Hepatology 2009; 50: 227-42
** Br J Haematol 2007; 136: 699
Algorithm for the prevention of reactivation of hepatitis B infection

All patients being considered for chemotherapy to be screened for serum HBsAg and anti-HBc

- **HBsAg+**
  - Check HBV DNA
  - **HBV DNA <2000 IU/ml**
    - Assess as a candidate for long term treatment rather than prophylaxis
  - **HBV DNA >2000 IU/ml**
    - At risk of reactivation
      - Lamivudine* 7 days prior to chemotherapy and for 6-12 months after cessation

- **HBsAg- anti-HBc+**
  - Prophylaxis not required

- **HBsAg- anti-HBc-**
2. Haemodialysis patients and allograft recipients

- HVB and HCV are the main responsible for the hepatic decompensation in this population
- After renal transplant (RT) these viruses have a deleterious effect in long survival and in the graft preservation

*Transplantation 2005; 79: 1132-6
HBV and renal disease

• In this population
  – High percentage of reactivation
  – High viral replication
  – Less spontaneous seroconversion
• Reduction of HBV prevalence mainly (> 90%) due to vaccination and EPO
• Acute HBV infection often subclinical but with evolution to chronicity in 80%
• Portugal: 45% before 1985 / 5% in 2005
HBV and Renal Transplant

- With the immunosuppressive therapy – high risk of increased viraemia even in inactive carriers*
- If a patient is HBsAg+ - less survival after transplant – 5-10 X higher mortality due to hepatic disease

* Revue Francophone des Laboratoires 2008; 403: 31-40
Haemodialysis patients
HBV

• Therapeutic attitude
  – HBV screening
    • Negative – vaccination
    • Positive – other serological markers / DNA-HBV

• HBV DNA positive and if it is a RT candidate
  – Treat HBV to avoid viral replication with oral drugs (ETV)*

* Hepatology 2009; 50: 227-42
Allograft recipients
HBV

• Therapeutic attitude
  – If they are under oral treatment – continue
  
  – If not (HBV-DNA negative)
    • initiate immediately* or/when reactivation**
      - *stop therapy > 2 yrs if HBV DNA undetectable(?)
      - **if reactivation – therapy for life
HCV and renal disease

• HCV is the main cause of hepatic disease in haemodialysis patients and allograft recipients
• Well known risk of nosocomial transmission
• Prevalence – 3 – 80% (related with duration of dialysis/different dialysis units)
• Portugal - 1990’ 60% of incidence
  - 2005 6,7% =
Outcome of HCV in dialysis patients

- The majority of patients have mild disease
- Evolution to cirrhosis and HCC is rare (indolent evolution)
- After RT the outcome is worse*
  - Colestatic hepatitis
  - More progressive hepatic disease (high risk of cirrhosis > 5 yrs)
  - Higher risk of other complications

*Hepatology 2002; 36: 206-10
Haemodialysis patients
HCV

Therapeutic attitude

• **When to treat?**
  – If high ALT and RNA-HCV +, consider liver biopsy and treat HCV before transplant
  – If cirrhosis is documented – treatment should not be performed

• **How to treat?**
  – PEGIFN alfa 2a – 135 mic/gr/weekly
  – PEGIFN alfa 2b – 1 mic/gr/weekly
  – Role of Ribavirin (close monitoring)
Allograft recipients
HCV

• Therapeutic attitude
  – Low efficacy
  – Increased risk
  – Interferon is not recommended (risk >50% of allograft rejection)
  – Other oral drugs- improve biochemical markers but not viraemia or histology
3. Liver transplant recipients

- Virus recurrence after Liver Transplant (LT) is high due to the presence of virus in extrahepatic sites (i.e. mononuclear cells)
  - HCV - major cause of LT in U.S.A.
  - Less frequent:
    - HBV - mainly cirrhosis and hepatocellular carcinoma
    - HBV+HDV
3. Liver transplant recipients

HBV

- HBV as a cause of LT has decreased due to
  - Vaccination
  - New oral drugs (nucleos(t)ides)
- The risk of reactivation is > 80% (initial hepatic disease / level of replication)
- Therapeutic attitude
  - DNA-HBV undetectable
    - Oral drug +/- HBIg
  - DNA-HVB detectable
    - Oral drug+HBIg (< 10% of recurrence)
3. Liver transplant recipients

HBV

HBIG schedules
• 10,000 U pre-OLT
• 10,000 U daily during 7 days
• 10,000 U e.v. weekly (1 mo), than monthly*
-----------------------------------------------------------------
• 10,000 U e.v. pré-OLT
• 1,000 U e.v. / i.m. daily during stay in LT Unit
• 1,000 U e.v. weekly (1 mo), than monthly**
-----------------------------------------------------------------
- main goal: maintain HBsAb titer > 500 IU/ml

*NEJM 1993; 329: 1842-7
** Hepatology 1996; 24: 1327-33
3. Liver transplant recipients

HCV

- LT is the only therapeutic option in HCV individuals with decompensation cirrhosis and hepatocellular carcinoma.
- Recurrence of HCV virus after LT is almost 100% (early).
- Immunosuppressive treatment (essential to avoid allograft rejection) accelerate the evolution of fibrosis.
3. Liver transplant recipients

HCV

• The HCV evolution in recipient is variable, ranging from mild disease to severe fibrosis and risk of development of cirrhosis in 2-5 yr > LT

• Level of HCV viraemia (pre-OLT) is the most important negative prognostic factor (more severe recurrence and higher resistance to treatment)

• Other prognostic factors include: age of donor > 55 yr, male, black, genotype 1, “early hepatitis” in the draft and high HCV RNA at 4th month

*Current Opinion Organ Transplantation 2005; 10: 81-9
** J Hepatol 2005; 43: 53-9
3. Liver transplant recipients

HCV

- HCV treatment should be offer pre-transplant
  - SVR < 50%
  - 30 patients – 30% SVR (Forns*)
  - 102 cirrhotic patients – 20% SVR (Everson**)

* J Hepatol 2003; 39: 389-96
** Hepatol 2002; 36: A 297
3. Liver transplant recipients
HCV

• Therapeutic attitude
  – PEGIFN alfa 2a/2b + Ribavirin – 24 weeks
    • 1 month after LT, if no contraindication
    • At the moment of “established” hepatitis in the alograft
4. HIV positive patients
Mortality and hepatic disease

Co-infected patients co-infectados – HIV/HCV

Mortality (%)

- France (Nice) 1: 2%
- Spain (Madrid) 2,3: 5%
- USA (Boston) 4: 12%
- Pre-HAART era
- HAART era

Prevalence of HIV/HBV Co-infection

- Among 9,803 subjects in the EuroSIDA Cohort:
  - 5,883 (60%) had an HBsAg test at the time of enrolment
  - 530 (9%) were positive

Regions:
- South: 9.7%
- Central: 9.2%
- North: 9.1%
- East: 6%

HIV/HBV – how they interact?

- High levels of DNA-HBV
- Less spontaneous recovery after acute hepatitis
- Higher evolution to chronicity
- Less “e” and “s” seroconversion
- Normal or mild elevated transaminases
### Liver related mortality in a cohort of 5293 patients, 1984/1987 - 2000

<table>
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<th>Nº</th>
<th>viral status</th>
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<th>Death p (1000/year)</th>
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<tr>
<td>139</td>
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<tr>
<td>5293</td>
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<td>+</td>
<td>62</td>
</tr>
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</table>

**Mortality**

18 X HIV/HBV vs HBV

HAART and impact on HBV

- Double action against HIV and HVB
- Less cases of acute HBV infection
- “e” and “s” seroconversion increased
- Improvement in histology and slow progression to cirrhosis and ESLD

* Lam-Kellerman SE. JID. 2003; 188. 571-7
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Target</th>
<th>Condition</th>
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<tbody>
<tr>
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<td>HBV</td>
<td>e+/e-</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>HBV/HIV</td>
<td>e+/e-</td>
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<td>Adefovir dipivoxil</td>
<td>HBV</td>
<td>e+/e-/lam-R</td>
</tr>
<tr>
<td>Entecavir</td>
<td>HEV (HIV?)</td>
<td>e+/e-/lam-R</td>
</tr>
<tr>
<td>Peg IFN alfa-2a</td>
<td>HBV</td>
<td>e+/e-/lam-R</td>
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<tr>
<td>Telbivudine</td>
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<td>Tenofovir</td>
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<td>e+/e-/lam-R</td>
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<tr>
<td>Emtricitabine</td>
<td>HIV/HBV</td>
<td>e+/e-</td>
</tr>
</tbody>
</table>
Treatment Algorithm:
Patients with Compensated Liver Disease and No indication for HIV therapy
(CD4 count > 350/µl)

HIV/HBV*

HBV DNA <2,000 IU/mL **
• No treatment
• Monitor every 6-12 months

HBV DNA ≥2,000 IU/mL
• Monitor ALT every 3-12 months
• Consider biopsy and treat if disease present***

ALT Normal
• PEG IFN**** (favorable response factors are: HBeAg+ - HBV Genotype A – elevated ALT and low HBV-DNA)
• Telbivudine (if HBV-DNA is still detectable at week 24 add adefovir to minimize resistance development risk)
• Adefovir and telbivudine de novo therapy
• Early HAART initiation including Tenofovir+3TC/FTC

ALT Elevated

**Soriano V, et al. 4th IAS, Sydney 2007, #MoBS104; Benhamou Y, 3rd International Workshop on HIV and hepatitis coinfection, Paris 2007**
Immediate indication for HIV treatment

- **HBV-DNA ≥ 2000 IU/ml**
  - Patients without HBV associated 3TC resistance
    - HAART including TDF + 3TC or FTC
  - Patients with HBV associated 3TC resistance
    - HAART regimen of choice
    - Substitute one NRTI by Tenofovir or add Tenofovir*
- **HBV-DNA < 2000 IU/ml**
- **Patients with cirrhosis**
  - HAART including TDF + 3TC or FTC
    - Refer patient for liver transplantation evaluation if liver decompensation occurs

*if feasible and appropriate from the perspective of maintaining HIV suppression

*ECC Statement J Hepatol 2005*
HIV/HCV co-infection

HIV
40 million

HCV
145 million

HIV/HCV
5 million

Alter MJ. J of Hepatology. 2006
UNAIDS, WHO. 2006
Treating HCV is Increasingly Important for Improved Survival in HIV/HCV-Coinfected Patients

• HCV coinfection adversely impacts HAART efficacy
  - Increased risk of antiretroviral drug-associated hepatotoxicity and drug discontinuation
  - Decreased likelihood of CD4+ cell increases during HAART

• HIV accelerates time to HCV-related liver disease
  - Faster time to cirrhosis
  - Faster time to HCC

3. Mohsen A. Gut. 2003
HIV influence

914 HIV/HCV patients with CCH and elevated ALT

- < 30 years: 62% (F0-F1: 15, F3-F4: 15)
- 31-40 years: 44% (F0-F1: 35, F3-F4: 32)
- > 41 years: 46% (F0-F1: 46, F3-F4: 46)

HIV influence

- Higher HCV RNA
- More rapid progression of the disease (i.e. fibrosis)
- Higher incidence of hepatocellular carcinoma in young age
- 25% of co-infected individuals develop cirrhosis in 15 years (vs 5% in VIH-)*

*Sanchez QA, EJCMID, 1995; 14:949-53
HCV treatment – ideal candidate?

- All co-infected patients with detectable HCV RNA
- CD4 > 350 cells/mm³
- Individualize treatment
- Take into account other factors
HCV treatment

PEGIFN alpha 2a/2b/weekly

+ 

Ribavirin 1000 or 1200 mg/daily (< 75 >Kg)
Current Algorithm for HCV Therapy in HIV Co-infected Patients

W4

W12

G2/3†

G1/4

HCV RNA neg

HCV RNA pos

>2 log drop in HCV RNA

<2 log drop in HCV RNA

W24

24 weeks' therapy*

48 weeks' therapy

HCV RNA neg

G2/3

G1/4

72 weeks' therapy

HCV RNA pos

Stop

Stop

W48

W72


*In patients with baseline low viral load and minimal liver fibrosis.

†G1–G4 refer to genotypes 1–4
Drug interactions

- Didanosine - **Contraindicated**
- Zidovudine – avoid
- Stavudine - avoid
Conclusions

- **Important messages:**
  - Immunosuppression facilitates hepatitis reactivation, chronicity and histological impairment
  - Early recognition of these conditions is crucial
  - Prophylactic and therapeutic measures should be taken to ameliorate the prognosis of these patients