Hepatitis E virus in immunocompromised patients

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- Grants: BMS, Gilead, Roche, MSD

Nothing to disclose for this presentation
HEV infection in the immunocompetent patient

- HEV RNA is detected in the stools during the icteric phase and usually persists 10 days to 1 month

- Disappearance of HEV RNA:
  - Administration to a volunteer: 16 days after the beginning of jaundice
  - Usually up to 45 days (112 days rare but described)

Spontaneous resolution of HEV infection is the rule in immunocompetent patients
HEV infection in immunocompromised patients

Chronic HEV infection

• Epidemiology of HEV infection

• Treatments of HEV infection
HEV infection in immunocompromised patients

Chronic HEV infection

• Epidemiology of HEV infection

• Treatments of HEV infection
HEV infection in immunocompromised patients

Chronic HEV infection

- Chemotherapy of malignancies
  - Solid organ transplantation
  - Other immune deficiencies
- HIV infection
Chemotherapy

Autologous bone marrow transplantation

HEV RNA negative

10 months

Péron JM J Gastroenterol Hepatol 2006
HEV and haematological malignancies

- 299 patients from Nov 2003 to Dec 2008 in Hematology

Elevated transaminases

- Screened for HEV:
  - In house RT-PCR (J Izopet, Purpan Hospital Virology Unit)
  - IgG and IgM (Abbott HEV EIA, Laboratoire Abbott, Rungis, France)

HEV and haematological malignancies

- Hepatitis E in 6 patients (1 T-anaplastic large cell lymphoma/2 acute myeloid leukemia/2 mantle cell lymphoma/1 myeloma)

- No symptoms in 5; jaundice in one

- High transaminases levels in all patients: AST 504 UI/L (110-2309), ALT 672 UI/L (261-4273)

- HEV antibodies present in only 2/6 patients

- HEV viremia > 6 months in 3 patients (186, 270, 360 days) but viral clearance occurred in all patients with time

HEV and haematological malignancies

- One patient had a pre-cirrhotic stage on liver biopsy (F3)

- Transmission from one patient to another: 97.8-98.6% homology in HEV3 nucleotides sequences

- Chronic hepatitis E with cirrhosis in a patient with NHL treated by Rituximab

- 3 cases in children: 1 liver transplant recipient/1 BMT for medullar relapse of type B lymphoblastic leukemia/ 1 primary immunodeficiency due to XIAP deficiency
HEV infection in immunocompromised patients

Chronic HEV infection

• Chemotherapy of malignancies

• Solid organ transplantation

• Other immune deficiencies

• HIV infection
HEV infection and transplantation

- 33 acute hepatitis E (elevated transaminases levels and HEV RNA+ by RT-PCR in the serum or the stools)

- among 854 transplantations: Incidence = 3.86% between 01/01/2004 and 31/12/2008 (0.8%/year)

- All were autochthonous and genotype 3
- No symptoms: 17/27 (63%)/Asthenia, arthralgia, myalgia, one jaundice
- Elevated transaminases 2 X N

Kamar et al. NEJM 2008
27 of the 33 HEV+ patients had a follow-up > 6 months:
- 11 patients (41%): HEV clearance and maintained during a 22 (6-56) months follow-up:
  - Resolutive acute hepatitis E

• 16 patients (59%): persistence of HEV viremia and elevated transaminases levels with a 27 (7-96) months follow-up:
  - Chronic hepatitis E
HEV infection and transplantation

- Chronic hepatitis (HEV RNA + > 6 months): n = 16
  - 4 liver transplant recipients (25%) achieved viral clearance at 14, 16, 22 and 23 months
  - 12 (75%) still HEV RNA+ at 22 months (7-96)
- HEV serology (IgG+)
  - At diagnosis: n = 4 patients (25%)
  - At 6 months: n = 5 patients (31.25)
  - At last follow-up: 81.25%

Kamar et al NEJM 2008
HEV infection and transplantation

- **Hepatic manifestations:**

  Fibrosis/3 patients developed cirrhosis, including 2 liver-related deaths

- **Neurological manifestations:**

  Kamar et al. Emerging Inf Dis 2011

- **Renal manifestations:**

  Kamar et al. Transplantation 2012

  Gérolami et al. 2008
  Haagsma et al. Liver Transplant 2008
  Haagsma et al. Liver Transplant 2009
  Pischke et al. Liver Transplantation 2009
HEV infection and transplantation

85 pts with a FU > 6 months

29 cleared the virus within the 6 months after diagnosis:
   Acute hepatitis E (34.1%)
   No reactivation was observed

56 evolved to chronic hepatitis (> 6 months):
   Chronic hepatitis E (65.9%)

18 were cleared of the virus after immunosuppressant dose reduction (32.1%)

Kamar et al. Gastroenterology 2011
HEV infection and transplantation

Prediction of chronic hepatitis
Multivariate analysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR</th>
<th>CI&lt;sub&gt;95%&lt;/sub&gt;</th>
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</thead>
<tbody>
<tr>
<td>At diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count</td>
<td>1.02</td>
<td>1.001–1.1</td>
<td>0.04</td>
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<td>CSA / Tacrolimus</td>
<td>1.87</td>
<td>1.49–1.97</td>
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</table>
HEV infection and transplantation
Plasma and blood contamination

ALT level IU/L

HEV: Hepatitis E Virus
PE: Plasma exchange
PT: Plasma transfusion
RBCT: Red blood cell transfusion
RT: Renal transplantation

Mallet et al. Works in progress 2013
HEV infection and transplantation

- 347 kidney recipients, including 14% with therapeutic plasma exchange
- 31% anti-HEV IgG+, including 10% post-Tx de novo infection

RR PE* = 2.62
95% CI: 1.09-6.31

* Despite SD or Amotosalem inactivation

Mallet et al. Works in progress 2013
HEV infection in immunocompromised patients

Chronic HEV infection

• Chemotherapy of malignancies

• Solid organ transplantation

• Other immune deficiencies

• HIV infection
HEV infection in immune deficiencies

62-year-old man with chronic HEV infection
Cirrhosis and LYP

LYP SINCE DEC 2005

RBV: Ribavirin
PegIFN: Pegylated Interferon alpha
LYP: Lymphomatoid Papulosis
ALT: Alanine aminotransferase
HEV: Hepatitis E Virus

PegIFN

LYP RELAPSE

ALAB (x ULN)

Aug-08 Feb-09 Sep-09

HeV RNA

Jun-12 Dec-12 Jul-13
HEV infection in immune deficiencies

62-year-old man with chronic HEV infection
Cirrhosis and LYP

LYP SINCE DEC 2005

RBV

PegIFN

RBV

LYP REMISSION

LYP RELAPSE

LYP REMISSION

LYP RELAPSE

RBV: Ribavirin
PegIFN: Pegylated Interferon alpha
LYP: Lymphomatoid Papulosis
ALT: Alanine aminotransferase
HEV: Hepatitis E Virus

HEV RNA

ALT (x ULN)
Dapi
Lumière blanche
CD3
CD3 VHE
VHE
Dapi CD3
HEV infection in immunocompromised patients

Chronic HEV infection

- Chemotherapy of malignancies
- Solid organ transplantation
- Other immune deficiencies
- HIV infection
<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Patients tested</th>
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<tr>
<td>Balayan 1997</td>
<td>Russia</td>
<td>117</td>
<td>11.1%</td>
</tr>
<tr>
<td></td>
<td>Belarus</td>
<td>20</td>
<td>0%</td>
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<tr>
<td>Fainboim 1999</td>
<td>Argentina</td>
<td>484</td>
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</tr>
<tr>
<td>Renou 2010</td>
<td>South East France</td>
<td>133</td>
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<td></td>
<td>Northern France</td>
<td>112</td>
<td>3%</td>
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<tr>
<td>Kaba 2011</td>
<td>South East France</td>
<td>184</td>
<td>3.3%</td>
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<td>Maylin 2012</td>
<td>Paris France</td>
<td>261</td>
<td>1.5%</td>
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<td>Kenfak-Foguena 2011</td>
<td>Switzerland</td>
<td>735</td>
<td>2.6%</td>
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<td>Jardi 2012</td>
<td>Barcelona Spain</td>
<td>238</td>
<td>9%</td>
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<tr>
<td>Keane 2012</td>
<td>South West England</td>
<td>138</td>
<td>9.4%</td>
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<tr>
<td>Crum-Cianflone 2012</td>
<td>USA</td>
<td>194</td>
<td>3%</td>
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HEV infection in HIV-infected patients

Acute hepatitis E

- From 1985-2009, among 4410 HIV-infected persons, 458 (10%) had increased ALT levels (> 5N)

- All stored samples at ALT flare (42%) tested for IgM, IgG (Diagnostics Systems, Nizhniy Novgorod, Russia) and HEV RNA by PCR

HEV infection accounted for 4% of acute liver abnormalities among HIV-infected patients

No chronic infection

HEV is a cause of liver abnormalities in HIV-infected persons but is not more frequent than in the general population

Crum-Cianflone N et al Emerg Infect Dis 2012
HEV infection in HIV-infected patients

Chronic hepatitis E

- CD4 cell count < 200 cells
- Serological testing: unreliable
- Liver biopsy: cirrhosis

Dalton et al. NEJM 2009
HEV infection in HIV-infected patients
Chronic hepatitis E

- CD4 cell count < 200 cells
- Serological testing unreliable
- Liver stiffness 9 kPa (significant fibrosis)

HEV infection in immunocompromised patients

Chronic HEV infection

• Epidemiology of HEV infection

• Treatments of HEV infection
HEV infection and transplantation
Interferon therapy

Peg-interferon-α 2a 135 ug/week, 3 months
- HEV RNA detected from 2000 to 2010
- Absence of antibodies despite persistent viremia
- CD4 cell count < 200 cells/mm³

Singh et al. J Infect 2012

- SVR after 24 weeks of Peg-IFN-a-2a 180 mcg/kg
- weekly
- HEV RNA undetectable
- after 4 weeks of
- Peg-IFN-a-2a
HEV infection and transplantation
Ribavirin therapy

- 2 patients: SVR$_{24}$ (a late relapse)

HEV infection and transplantation
Ribavirin therapy

66% SVR

Figure 1. Serum hepatitis E virus RNA concentrations before and during the study period.
Hepatitis E virus treated patients: N= 59

Ribavirin therapy ≤ 3 months: N=39

SVR: N=29 (74.3%)
Relapsers N= 10

Ribavirin therapy > 3 months: N=20

SVR: N=17 (85.0%)
Relapsers N= 3

78% SVR 25 (6-42) months

Kamar et al. NEJM 2013

- RBV median dose: 600 (200 mg/week–1200 mg/day)= 8.1 (0.6–16.3) mg/kg/d
- Baseline lymphocyte count is the only predictor of SVR
HEV infection and transplantation
Interferon & Ribavirin combination

HEV infection in immunocompromised patients

Conclusions

- HEV infection markers should be included in the diagnostic workup of elevated transaminases in immunocompromised patients

- PCR based detection of hepatitis E viral RNA is essential to make the diagnosis

- There is a risk of patient to patient, blood transfusion or plasma transmission of HEV: plasma pools should be tested for HEV
HEV infection in immunocompromised patients

Conclusions

- Chronic HEV infection may occur with a risk of evolution towards cirrhosis (and extra-hepatic manifestations?)

- First line therapeutic approach: reduce doses of immunosuppressive drugs such as tacrolimus

- Second line therapeutic approach should be ribavirin with rescue with PEG/RBV
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