Hepatitis E virus infection in dialysis and transplant-patients

Pr Nassim KAMAR

Department of Nephrology, Dialysis, and Organ Transplantation
Toulouse University Hospital
France
Hepatitis E virus

- ARN virus, 7.2 kb genome

- 4 genotypes:
  - Genotype 1 (mainly in Asia, Africa and south America)
  - Genotype 2 (mainly in Mexico, and Africa)
  - Genotype 3 (mainly in western countries)
  - Genotype 4 (mainly in China, Japan, Taiwan)

- Endemic in developing word

- Sporadic and locally acquired cases in developed word.

⇒ Emerging disease

1 Emerson, Rev Med Virol 2003
2 Clemente-Casares, Emerg Infec Dis 2003
3 Dalton, Lancet Infect Dis 2008
HEV transmission

- Faecal-oral route +++ for genotypes 1 and 2 $^{1,2}$

- Consumption of animal products for genotype 3

- Other rare cases of HEV transmission:
  
  - transfusion $^{3,4,5}$
  
  - nosocomial transmission in a haemodialysis unit and in a haematology ward $^6,7$

- Mother to child transmission (vertical transmission) $^8$

$^1$ Emerson, Rev Med Virol 2003  
$^2$ Dalton, Lancet infect Dis 2008  
$^3$ Tamura, Hepatol Res 2007  
$^4$ Khuroo, J Gastro Hepatol 2004  
$^5$ Mitsui, J Med Virol 2004  
$^6$ Ayoola, J Med Virol 2002  
$^7$ Mansuy, CID 2009  
$^8$ Khuroo, Lancet 2005
HEV reservoir

- Zoonosis: anti-HEV ab have been detected in cats, dogs, cattle, sheep, goats, horses, macaques, donkeys, rats, and mice \(^1,2\)

- Transmission
  - Case Control study (Germany): Orfal, wild-boar meat \(^5\)
  - Higher seroprevalence among farmers (Denmark) \(^6\)
  - Transmission from a pet pig to its owner \(^7\)
  - HEV Transmission to a surgeon training on pigs \(^8\)
  - Consumption of game and uncooked meat \(^9\)

---

4. Rutjes, Emerg Infect Dis 2009
5. Wichmann, JID 2008
6. Christensen, CID 2008
9. Li, Emerg Infect Dis 2005
Raw pig liver sausage (Figattellu): A cause of HEV infection in Sout-East France

Colson et al. J Infect Dis 2010
Seroprevalence of IgG anti-HEV in blood donors

- Broutouille et al, *J Clin Microbiol* 2007: 2.91 / 3.50%
- 3% Tokyo
- 7.3% Spain (Catalonia)
- 16% South-West England
- 21.3% USA

*Dalton, Lancet Infect Dis* 2008
HEV seroprevalence in dialysis patients

**Europe:**
- Spain: 6.3%
- France: 11 to 14.5%
- Greece: 4.8 to 8.7%
- Ireland: 0%
- Italy: 3 to 9.3%
- Sweden: 6%

**Asia:**
- Saudi Arabia: 4.8%
- Iran: 7.4%
- Japan: 9.4 to 19%
- Taiwan: 31%

**Africa:**
- Egypt: 39.6%

Seroprevalence between 0 and 39.6%
Different forms of HEV infection

- **Acute hepatitis:**
  - resolving hepatitis \(^1,^2\)
  - **Fulminant hepatitis**
    - Patients with chronic liver disease \(^3\)
    - Pregnant women \(^4\)

- **Chronic hepatitis**
  - Solid organ-transplant (SOT) patients \(^5\)
  - HIV-positive patients \(^6\)
  - Haematological patients \(^7\)

---

2. Dalton et al., Lancet Infect Dis 2008
3. Peron et al., J Viral Hepatitis 2007
4. Kumar et al., Int J Gynaecol Obstet 2004
5. Kamar et al., NEJM 2008
6. Dalton et al., NEJM 2009
Definition of chronic HEV infection

- There is no established definition for chronic HEV infection

- Definition used in published literature:
  - Persisting elevated liver-enzyme levels
  - Positive HEV RNA in the serum and/or in the stools
  - 6 months after diagnosis
Hepatitis E virus infection in solid-organ-transplant patients
Between 2004 and 2008, organ donors were tested for anti-HEV IgG: \( N = 258 \)

- 35/258 were tested positive for anti-HEV IgG
- 15/258 were tested positive for anti-HEV IgM (HEV RNA negative)

⇒ Seroprevalence in organ donors = 13.5%

No HEV transmission by the graft or by blood transfusion

- Organ donors of 15/17 SOT who presented with HEV infection within the first year posttransplantation were tested for HEV:
  - 14 were anti-HEV IgG - / Ig M -
  - 1 was anti-HEV IgG - / Ig M + (HEV RNA -)

- Among 34 SOT with HEV infection, 2 had receive blood transfusion within the 3 months before acute HEV episode. The 10 invloved blood donors were tested for HEV:
  - 9 were anti-HEV IgG - / Ig M -
  - 1 was anti-HEV IgG - / Ig M +
  - All 10 were HEV RNA -

HEV Seroprevalence and incidence in SOT patients (Toulouse)

Patients undergoing KT, LT or SKP between 2004-2008
n=700

Follow-up until December 2009

Anti-HEV IgG + Anti-HEV IgM - HEV RNA -
n=82

Median FU: 22 mo

HEV RNA positive: none
No reactivation

Anti-HEV IgG + Anti-HEV IgM + HEV RNA -
n=7

Anti-HEV IgG - Anti-HEV IgM + HEV RNA -
n=10

Anti-HEV IgG - Anti-HEV IgM -
n=601

Median FU: 22 mo

Anti-HEV seroconversion: 14 HEV RNA +: 20
34 de novo infections

HEV Seroprevalence and incidence in SOT patients (Toulouse)

Patients undergoing KT, LT or SKP between 2004- 2008
n=700

Follow-up until December 2009

Anti-HEV IgG +
Anti-HEV IgM -
HEV RNA -
n=82

Anti-HEV IgG +
Anti-HEV IgM +
HEV RNA -
n=7

Anti-HEV IgG -
Anti-HEV IgM +
HEV RNA -
n=10

Anti-HEV IgG -
Anti-HEV IgM -
n=601

HEV Seroprevalence
- 89 / 700 were tested positive for anti-HEV IgG: 12.7%
- 68/529 kidney-transplant patients: 12.9%
- 21/171 liver-transplant patients: 12.3%

No reactivation

Anti-HEV seroconversion: 14
HEV RNA +: 20
34 de novo infections

HEV Seroprevalence and incidence in SOT patients (Toulouse)

Patients undergoing KT, LT or SKP between 2004-2008
n=700

Follow-up until December 2009

<table>
<thead>
<tr>
<th>Anti-HEV IgG</th>
<th>Anti-HEV IgM</th>
<th>HEV RNA</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>-</td>
<td>-</td>
<td>82</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>-</td>
<td>7</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>-</td>
<td>10</td>
</tr>
</tbody>
</table>

Median FU: 22 mo

HEV RNA positive: none
No reactivation

HEV RNA positive: none
Anti-HEV IgG - Anti-HEV IgM -
n=601

Median FU: 22 mo

Anti-HEV seroconversion: 14
HEV RNA +: 20
34 de novo infections

HEV Seroprevalence and incidence in SOT patients (Toulouse)

Patients undergoing KT, LT or SKP between 2004-2008
n=700

Follow-up until December 2009

Incidence:
- Overall: 3.2 cases/100 person-years
- Kidney-transplant: 2.7 cases/100 person-years
- Liver-transplant: 4.8 cases/100 person-years

P=0.09

HEV RNA positive: none
No reactivation

Anti-HEV IgG -
Anti-HEV IgM -
n=601

Anti-HEV seroconversion: 14
HEV RNA +: 20
34 de novo infections

Median FU: 22 mo

Prevalence and incidence of HEV infection in liver-transplant patients (The Netherlands)

Eligible: 331 patients
Available: 285 patients' sera (85%)

- Negative HEV parameters: 274 patients (96.1%)
- HEV RNA positive: 1 patient with chronic hepatitis E
- HEV IgG positive: 9 patients
  - Seropositive since pretransplant: 6 patients
  - Posttransplant episode of HEV infection: 1 patient
  - Seropositive some time after transplantation: 2 patients
- HEV IgM positive: 1 patient

Incidence ≈ 2%

Haagsma et al., Liver Transplant 2009
HEV seroprevalence in liver-transplant patients (Germany)

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of Patients</th>
<th>Anti-HEV IgG–Positive</th>
<th>Anti-HEV IgM–Positive</th>
<th>HEV RNA–Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy controls</td>
<td>108</td>
<td>1 (0.9%)</td>
<td>0/1*</td>
<td>0/1*</td>
</tr>
<tr>
<td>Nontransplanted patients with chronic liver disease</td>
<td>108</td>
<td>4 (3.1%)</td>
<td>1 (0.8%)</td>
<td>1/129 (0.8%)</td>
</tr>
<tr>
<td>Liver transplant recipients with no graft hepatitis (group A)</td>
<td>156</td>
<td>7 (4.5%)</td>
<td>0 (0%)</td>
<td>0/156 (0%)</td>
</tr>
<tr>
<td>Liver transplant recipients with elevated ALT levels (group B)</td>
<td>70</td>
<td>3 (4.3%)</td>
<td>2 (2.9%)</td>
<td>2/70 (2.9%)</td>
</tr>
</tbody>
</table>

Pischke et al., Liver Transplant 2010
HEV seroprevalence in kidney and liver-transplant patients (Spain)

- Between July and August 2008, 108 kidney- or liver-transplant recipients were tested for HEV
  - 82 liver-transplant recipients
  - 21 kidney-transplant recipients
  - 5 dual-organ recipients

- Anti-HEV IgG was detected in only 3/108 patients (2.1%)
Case control study to investigate the source of contamination in solid-organ-transplant patients

- 37 SOT patients matched to 148 other SOT patients for age and gender
- Questionnaire: living conditions, food, drink, and leisure activity

<table>
<thead>
<tr>
<th></th>
<th>Case subjects (%)</th>
<th>Control subjects (%)</th>
<th>P</th>
<th>Odds Ratios (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bivariate analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eating game meat</td>
<td>67%</td>
<td>47%</td>
<td>0.03</td>
<td>2.3 (1.04-5.22)</td>
</tr>
<tr>
<td>Eating pork product</td>
<td>97%</td>
<td>83%</td>
<td>0.03</td>
<td>6.82 (0.86 -53.9)</td>
</tr>
<tr>
<td>Eating mussels</td>
<td>100%</td>
<td>77%</td>
<td>0.002</td>
<td>10 (1.25 -79.7)</td>
</tr>
<tr>
<td><strong>Multivariate analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eating game meat</td>
<td>67%</td>
<td>47%</td>
<td>0.03</td>
<td>2.3 (1.04 -5.22)</td>
</tr>
</tbody>
</table>

Natural history of HEV infection in solid-organ transplant patients

- Multicenter study: 17 centers in Europe and 1 in USA
- 85 solid-organ-transplant patients

- Toulouse (n= 52);
- Groningen (The Netherlands, n=5);
- Montpellier (n= 4);
- Hannover (Germany, n=3);
- Lyon (Edouard Herriot n=3);
- Lille (n=3);
- Nice (n=2);
- Necker (n=2);
- Saint Antoine (n=2);
- Pitié Salpétrière (n=2);
- Royal Cornwall Hospital (UK, n=1);
- Sioux Falls (USA, n=1);
- Saint Luc Hospital (Belgium, n=1);
- Limoges ( n=1);
- Dijon ( n=1);
- Lyon Nord Croix Rousse  n=1);
- Paul Brousse (n=1).

- Kidney (n= 47);
- Liver (n=26);
- Liver-kidney (n= 2);
- Kidney-pancreas (n=6);
- Islet (n=1);
- Heart (n=2);
- Lung (n=1).

Kamar et al., Gastroenterology 2011
Clinical and biological at diagnosis

- Only 32% were symptomatic (fatigue+++)
- 35% had contact with animals
- Anti-HEV IgG: 78 tested, 41% positive
- Anti-HEV IgM: 78 tested, 80.8% positive
- HEV RNA: 82 tested, 100% positive
- Genotype 64 tested. 59 genotype 3 (5 not amplified)
- ALT: 260 ± 38 IU/L (vs. 42 ± 8, p <0.0001)
- AST: 155 ± 25 IU/L (vs. 29 ± 3, p<0.0001)
- γGT: 308 ± 56 IU/L (vs.90 ± 20, p<0.0001)
- Total bilirubin: 22.5 ± 3.8 µmoL/L (vs. 11.2 ± 0.8, p=0.005).
Outcome

85 pts with a FU > 6 months

29 cleared the virus within the 6 Months after diagnosis:
Acute hepatitis E (34.1%)

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

No reactivation was observed

Chronic hepatitis rate:
- Toulouse: 57.8%
- Outside Toulouse: 78.8%

Kamar et al., Gastroenterology 2011
Factors associated with the development of chronic hepatitis

N=14

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients with Resolving Infection (N = 6)</th>
<th>Patients with Chronic Infection (N = 8)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>median (range)</td>
<td>median (range)</td>
<td></td>
</tr>
<tr>
<td>At diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time since transplantation — mo</td>
<td>78.5 (25–168)</td>
<td>37.5 (6.0–63.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>Leukocyte count — x10^3/mm^3</td>
<td>8.85 (6–9.66)</td>
<td>4.31 (2.19–7.20)</td>
<td>0.004</td>
</tr>
<tr>
<td>Lymphocyte count — x10^3/mm^3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1.73 (1.12–2.33)</td>
<td>0.75 (0.63–1.04)</td>
<td>0.004</td>
</tr>
<tr>
<td>CD2+</td>
<td>1.59 (0.84–2.25)</td>
<td>0.66 (0.58–0.92)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CD3+</td>
<td>1.54 (0.70–1.88)</td>
<td>0.61 (0.49–0.79)</td>
<td>0.01</td>
</tr>
<tr>
<td>CD4+</td>
<td>0.93 (0.49–1.07)</td>
<td>0.22 (0.16–0.40)</td>
<td>0.004</td>
</tr>
<tr>
<td>Platelet count — x10^3/mm^3</td>
<td>261 (190–285)</td>
<td>155.5 (75.0–250.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Serum creatinine — mg/dl</td>
<td>2.15 (1.31–2.84)</td>
<td>1.33 (1.08–1.89)</td>
<td>0.01</td>
</tr>
<tr>
<td>At last follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase — IU/liter</td>
<td>25.5 (7–35)</td>
<td>55.5 (39.0–238.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Alanine aminotransferase — IU/liter</td>
<td>25 (13–45)</td>
<td>108.0 (59.0–298.0)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Kamar et al., NEJM 2008
### Predictive factors for chronic hepatitis: Multicenter study

#### Univariate analysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients with resolving HEV infection (n =29)</th>
<th>Patients with chronic hepatitis (n=56)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver/non-liver transplant</td>
<td>5/24</td>
<td>23/33</td>
<td>0.05</td>
</tr>
<tr>
<td>Time last AR /HEV (days)</td>
<td>102±93</td>
<td>29.5±31</td>
<td>0.03</td>
</tr>
<tr>
<td>Time since transplantation (m)</td>
<td>70.3±52.8</td>
<td>41.4±38</td>
<td>0.005</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>107 (16–1,571)</td>
<td>94 (21–436)</td>
<td>0.02</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>263 (24–2,675)</td>
<td>135 (28–874)</td>
<td>0.001</td>
</tr>
<tr>
<td>Peak AST level (IU/L)</td>
<td>223 (31–1,571)</td>
<td>147 (39–874)</td>
<td>0.001</td>
</tr>
<tr>
<td>Peak ALT level (IU/L)</td>
<td>272 (29–2,675)</td>
<td>167 (32–522)</td>
<td>0.005</td>
</tr>
<tr>
<td>Serum creatinine (µmol/L)</td>
<td>168±69</td>
<td>130±51</td>
<td>0.005</td>
</tr>
<tr>
<td>Platelet count (/mm3)</td>
<td>225,655±62,521</td>
<td>190,384±79,903</td>
<td>0.04</td>
</tr>
<tr>
<td>Cyclosporin A / Tacrolimus</td>
<td>9/13</td>
<td>4/43</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*Kamar et al., Gastroenterology 2011*
Predictive factors for chronic hepatitis: Multicenter study

Multivariate analysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR</th>
<th>CI&lt;sub&gt;95%&lt;/sub&gt;</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count (/mm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>1.02</td>
<td>1.001–1.1</td>
<td>0.04</td>
</tr>
<tr>
<td>Cyclosporin A / Tacrolimus</td>
<td>1.87</td>
<td>1.49–1.97</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Kamar et al., Gastroenterology 2011
Impact of HEV on liver histology

- Resolving group (n=11)
  - 7/11 patients underwent a liver biopsy at diagnosis.
  - Activity score: 2 (0-3) Metavir units.
  - Fibrosis score: 1 (0-1) Metavir units

- 2/11 patients underwent a second liver biopsy after HEV clearance
  - Patient 1: A1F1 vs. A1F2 (10 months later). (recurrent HCV infection)
  - Patient 2: A2F1 vs. A0F1 (22 months later)

- Chronic group (n=16)
  - 1 to 5 liver biopsy/ patient.
  - Median time between first and last liver biopsy: 22 (10-96) months
  - Activity scores increased from 1 (1-2) vs. 2 (1-3) Metavir units (p= 0.08)
  - Fibrosis scores increased from 1 (0-2) to 2 (1-4) Metavir units (p=0.04)
  - 3 patients evolved to cirrhosis: (1 KT, 1 SKP, 1 LT)
  - 2 out of 3 : decompensated cirrhosis and portal hypertension and died (hemorrhagic shock, and a septic shock).

Kamar et al., Transplantation 2010
HEV-related cirrhosis

- 3 reported cases in kidney-or kidney-pancreas-transplant patients (Gérolami, NEJM 2008; Kamar, AJT 2008; Kamar, Transplantation 2010).

- 3 reported cases in liver-transplant patients (Haagsma, Liver transplant 2008; Kamar, Transplantation 2010).

- 8/85 (9.4%) in the multicenter study (Kamar et al., in press).

- Rapid progression to cirrhosis, especially in kidney-transplant patients (18, 22 and 38 months after acute phase). Faster than in HCV-positive KT patients.
Outcome of liver histology in patients with chronic hepatitis E virus infection who were cleared of the virus

- All were liver-transplant patients
- Patients underwent 3 to 5 liver biopsies (LBs).

<table>
<thead>
<tr>
<th></th>
<th>First LB at diagnosis</th>
<th>Last LB before HEV clearance</th>
<th>Last LB after HEV clearance</th>
<th>Time between diagnosis and last LB before HEV clearance (months)</th>
<th>Time between LBs before and after HEV clearance (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>A0F1</td>
<td>A3F2</td>
<td>A1F2</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Patient 2</td>
<td>A1F2</td>
<td>A2F2</td>
<td>A0F2</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td>Patient 3</td>
<td>A1F1</td>
<td>A2F3</td>
<td>A1F2</td>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td>Patient 4</td>
<td>A2F1</td>
<td>A2F1</td>
<td>A2F1</td>
<td>14</td>
<td>9</td>
</tr>
</tbody>
</table>

The lack of regression of liver fibrosis may be related to other causes than HEV, such as chronic allograft dysfunction

*Kamar et al., Transplantation 2010*
Management of chronic hepatitis E virus infection
Outcome

34 acute hepatitis E virus

7 pts with a FU < 6 months

27 pts with a FU > 6 months

11 cleared the virus within the 6 Months after diagnosis:

Acute hepatitis E (40.7%)

16 evolved to chronic hepatitis (> 6 months):

Chronic hepatitis E (59.3%)

4 were cleared of the virus after immunosuppressant dose reduction (15 to 24 months after diagnosis)

Kamar et al., Transplantation 2010
Differences between chronic patients who remained viremic and those with who were cleared of the virus

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients with chronic HEV infection who remained viremic (n = 12)</th>
<th>Patients with chronic HEV infection who were cleared off the virus (n = 4)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney or SKP/liver Tx organ</td>
<td>9/3</td>
<td>0/4</td>
<td>0.02</td>
</tr>
<tr>
<td>AST at last FU (IU/L)</td>
<td>72 (26-308)</td>
<td>17 (8-67)</td>
<td>0.03</td>
</tr>
<tr>
<td>ALT at last FU (IU/L)</td>
<td>99 (42-257)</td>
<td>16.5 (8-56)</td>
<td>0.005</td>
</tr>
<tr>
<td>Activity score at last LB</td>
<td>2 (1-3)</td>
<td>1 (0-1)</td>
<td>0.02</td>
</tr>
<tr>
<td>Induction therapy at Tx: Y/N</td>
<td>11/1</td>
<td>1/3</td>
<td>0.03</td>
</tr>
<tr>
<td>C0 Tac at last FU (ng/mL)</td>
<td>7.35 (3.8-11.2)</td>
<td>3.25 (2.5-6.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>Steroids (mg/kg/d) at last FU</td>
<td>0.1 (0.06-0.1)</td>
<td>0.035 (0.03-0.04)</td>
<td>0.04</td>
</tr>
<tr>
<td>CD3 + cells at last FU (/mm³)</td>
<td>427 (344-783)</td>
<td>1033 (440-1570)</td>
<td>0.05</td>
</tr>
<tr>
<td>CD4 + cells at last FU (/mm³)</td>
<td>261 (167-292)</td>
<td>369 (322-444)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Immunosuppressant dose reduction may be a first-line therapeutic option

Kamar et al., Transplantation 2010
Outcome: Multicenter study

85 pts with a FU > 6 months

29 cleared the virus within the 6 Months after diagnosis:
Acute hepatitis E (34.1%)

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
Pegylated-alpha interferon for chronic HEV infection
• Three liver-transplant patients with chronic HEV infection

• Pegylated interferon alpha-2a

• 135 µg/week

• Three months

• SVR: 2 out of 3

Kamar et al., Clin Infect Dis 2010
Liver-Transplant patient with chronic HEV infection

Peg IFN (27 mo after re-OLT) (9 years post-infection)
-100 µg for 4 weeks
- 80 µg for 16 weeks
- 60 µg for 32 weeks
-Total 52 weeks

No relapse 3 months after Peg-IFN

Haagsma et al., Liver Transplant 2010

Liver-Transplant patient with chronic HEV infection

Peg IFN (9 mo after OLT)
-150 µg for 4 weeks
- 120 µg for 4 weeks
- 90 to 100 µg for 8 weeks
-Total 16 weeks

HEV clearance at week 20 (4 weeks after Peg-IFN therapy).

Effect of Tac C0 decrease?
Hemodialysis patient with chronic HEV infection

Kamar et al., NDT 2010
Patient with hairy cell leukemia and chronic HEV infection

- Pegylated interferon alpha-2a
- 1 µg/kg/week
- Three months
- Sustained virological response

Alric et al., Ann Intern Med 2010
Ribavirin for chronic HEV infection
Ribavirin monotherapy for chronic HEV infection in SOT patients

- **2 patients:**
  - Ribavirin: 12 mg/kg/d
  - 3 months
  - HEV clearance: 2 patients, but short follow-up.
    
    * (Mallet, Ann Intern Med 2010)

- **8 patients,**
  - Ribavirin: 400 to 800 mg/d
  - 3 months
  - 6 patients with long FU: SVR in 4 patients
  - 2 patients with short FU: HEV clearance in 2 patients
    
    * (Kamar, Gastroenterology 2010)
Ribavirin monotherapy follow-up

- 12 patients: Kidney (n=9), Kidney-pancreas (n=1), Liver (n=1) & heart-transplant (n=1) patients with chronic HEV infection

- Ribavirin was given at the dose of 200 to 800 mg/d according to the calculated creatinine clearance for 3 months

- Time since transplantation at HEV infection: 33 (9-156) months

- Time between HEV infection and ribavirin therapy: 14.5 (5-46) months

- Follow-up after the end of antiviral therapy:
  - 10 patients had > 6 months FU after end of therapy
  - 2 patients were at end of therapy

Unpublished data
• 10 patients had > 6 months FU after therapy
  - SVR: 7 patients
  - Relapse: 3 patients
• 2 patients were cleared of the virus at the end of therapy
Virological response after 6 months ribavirin therapy in 2 relapsers

2 SVR
Prevention of HEV infection

- **Dietary measures**
  - Avoid undercooked meet, orfal, porc sausages.....

- **Vaccine**
  - GSK vaccine:
    - Phase II trial in ≈ 2000 male Nepalese Army recruits
    - Very good efficacy
    - Withdrawn from the development  *(Shrestha, NEJM 2007)*

  - Chinese vaccine (National Institute of Diagnostics and Vaccine Development in Infectious Diseases, Xiamen University):
    - Bacterially expressed recombinant hepatitis E vaccine (truncated section of ORF-2)
    - Phase III: 100,000 immunocompetent healthy adults in China
    - 30 µg, at months 0,1 and 6 vs. placebo
    - Efficacy (100%) and safety *(Zhu, Lancet 2010)*
Extra-hepatic HEV manifestations:

Neurological disorders
Neurological manifestations associated with acute HEV-infection

- Guillain-Barre syndrome \(^1,2\)
- Neuralgic amyotrophy (Parsonage Turner Syndrome) \(^3,4\)
- Acute transverse myelitis \(^5\)

The relationship between the neurological symptoms and HEV infection has been based on the detection of anti-HEV IgM (n=5) or HEV RNA (n=1) in the sera

1 Kamani, Indian J Gastroenterol. 2005
2 Loly, World J Gastroenterol. 2009
3 Fong, Clin Neurol Neurosurg. 2009
4 Rianthavorn, Scand J Infect Dis. 2010
5 Mandal, Indian Pediatr. 2006
Neurological symptoms in a transplant patient with chronic HEV-infection

- 44 years-old
- Kidney-transplant patient with chronic HEV infection
- Peripheral nerve involvement with proximal muscular weakness affecting the four limbs joint with central nervous system involvement
- HEV RNA in serum and CSF
- IV Ig
- No improvement
- Decompensated cirrhosis, and death from a hemorrhagic shock

Kamar et al., Am J Transplant 2010
HEV Genotype 3f, Genbank number FJ665423

Are neurological symptoms linked to the emergence of neurotropic variants?

Kamar et al., Am J Transplant 2010
Neurological symptoms and HEV infection

✓ Retrospective study between 2004-2009

✓ 126 patients with acute or chronic locally acquired genotype 3 HEV infection

✓ 2 countries:
  ▪ Toulouse (France):
    • Transplant unit: 50
    • Hepatology unit: 21
  ▪ Truro (UK):
    • Hepatology unit: 55

✓ Incidence of neurological disorders: 7/126 (5.5%)

Kamar et al., Emerg Infect Dis 2011
HEV may induce peripheral neurological symptoms

<table>
<thead>
<tr>
<th>Serum</th>
<th>CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEV IgG/IgM</td>
<td>HEV RNA</td>
</tr>
<tr>
<td>+</td>
<td>623</td>
</tr>
<tr>
<td>+</td>
<td>1160</td>
</tr>
<tr>
<td>+</td>
<td>384</td>
</tr>
<tr>
<td>+</td>
<td>171</td>
</tr>
<tr>
<td>+</td>
<td>110</td>
</tr>
<tr>
<td>+</td>
<td>105</td>
</tr>
<tr>
<td>+</td>
<td>150</td>
</tr>
</tbody>
</table>

**Neurological symptoms**

<table>
<thead>
<tr>
<th>Neurological symptoms</th>
<th>Therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute inflammatory polyradiculoneuropathy</td>
<td>-</td>
<td>Complete resolution</td>
</tr>
<tr>
<td>Bilateral brachial neuritis</td>
<td>-</td>
<td>Resolution with residual weakness</td>
</tr>
<tr>
<td>Guillain-Barré Syndrome</td>
<td>IV Ig</td>
<td>Resolution at HEV clearance</td>
</tr>
<tr>
<td>Ataxia, severe proximal weakness of his lower limbs, urine retention, and cognitive dysfunction</td>
<td>IS modification</td>
<td>Resolution with residual motor deficit</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>IS Stop, Foscavir, IV Ig</td>
<td>Complete resolution</td>
</tr>
<tr>
<td>Peripheral demyelinating polyradiculoneuropathy</td>
<td>IS modification, IV Ig</td>
<td>No improvement</td>
</tr>
<tr>
<td>Painful sensory peripheral neuropathy</td>
<td>Peg-IFN/ ribavirin</td>
<td>Complete resolution</td>
</tr>
</tbody>
</table>

*Kamar et al., Emerg Infect Dis 2011*
HEV infection may evolve to chronic hepatitis in immunosuppressed patients.

Characteristics of HEV infection in solid organ-tranplant patients:

- Majority of patients are asymptomatic.
- The increase of liver enzymes levels is less marked than in immunocompetent patients.
- Seroconversion is delayed and may never occur.
- Positive serum HEV RNA may persist for a long period.
HEV infection evolves to chronic hepatitis in nearly 60% of transplant patients.

HEV infection may evolve to cirrhosis and may recur after retransplantation.

The reduction of immunosuppressive drugs targeting T-cells should be considered as a first-line therapeutic option.

Pegylated-interferon therapy and ribavirin are efficient anti-viral therapies against HEV.

HEV induces neurological symptoms and kidney injuries.
Acknowledgments

Department of Nephrology, Dialysis, and Organ Transplantation
Rangueil Hospital
Toulouse

Pr L. Rostaing
Dr O. Cointault
Dr L. Esposito
Dr J. Guitard
Dr L. Lavayssière
Dr MB. Nogier
Dr D. Ribes

Department of Virology
Purpan Hospital
Toulouse

Pr J. Izopet
Dr F. Legrand-Abravanel
Dr JM. Mansuy

Department of Pathology
Toulouse University Hospital

Dr M. Danjoux
Dr J. Selves
Dr C. Guilbeau-Frugier

Department of Hepatology
Purpan Hospital
Toulouse

Pr L. Alric
Pr JM. Peron
Thank you for your attention