Liver and the Kidneys

APSN/HKSN CME Course
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Liver & the Kidneys

- **Liver & Kidneys** are two **vital** organs in the body
- **Disease in the liver** can have **significant impact on the kidneys**
- **Management of liver diseases** can be **challenging** in the face of renal failure

- **Viral hepatitis & kidneys**
  - Effect of viral hepatitis infection on kidneys
  - Management of chronic viral hepatitis infection (HBV, HCV & HEV) in renal failure patients

- **Hepatorenal syndrome (HRS)**
  - New insights on pathogenesis & management
  - Diagnosis & prediction
HBV & the Kidneys
HBV-associated membranous GN

• Spontaneous remission common in children but uncommon in adults

• Prognosis: 30% CKD; 10% ESRD after 5 yr FU

• Management
  – Poor response to IFN Rx;
  – Oral NA appeared to be effective (CR 40% & 60% at 6 & 12 months); 3-yr renal survival 100% vs. 58% (no Rx)
  – role of adding immunosuppressive Rx uncertain

Sin SK, et al. Kor J Nephrol 1999
Management of Chronic HBV infection in kidney transplant recipients
Chronic HBV infection in renal transplant recipients

- Chronic HBV infection associated with **adverse outcomes** in kidney transplant recipients (KTRs)

**Early Complications**
- Fulminant Hepatitis

**Late Complications**
- Cirrhosis
- Fibrosing cholestatic hepatitis
- Hepatocellular Carcinoma

Chan TM et al. Gastroenterology 1998
Fornairon S et al. Transplantation 1996
Cheung CY et al. Renal Failure 2014
Available options for HBV infection

- Interferon (IFN)
  - Low treatment efficacy
  - Precipitate graft dysfunction

- Oral nucleoside/tide analogues (NA)
  - Lamivudine (LAM)
  - Adefovir (ADV)
  - Entecavir (ETV)
  - Tenofovir (TDF)
  - Telbivudine (TBV)

Rostaing L et al. Nephron 1996
Durlik M et al. Transplant Int 1998
Anti-viral Rx in KTR

- Ideal antiviral Rx in KTR
  - High efficacy
  - Low resistance rates
  - Prevent short- and long-term hepatic complications!
  - Lack of nephrotoxicity (?Reno-protective effects)
Lamivudine (LAM) in KTR

• First oral NA available

• Most extensive efficacy and safety data in KTR

• Effectively suppress HBV DNA and improve LFT

• Meta-analysis (at 14 months):
  – HBV undetectability: 91%
  – HBeAg clearance (27%)
  – ALT normalization (81%)
  – LAM-resistance (18%)

• Long-term outcome data also available

• Relatively lower costs

Chan TM et al. Hepatology 2002
Chan TM et al. Am J Transplant 2004
Fabrizi F et al. Transplantation 2004
Fabrizi F et al. Am J Transplant 2005
Yap DY et al. Transplantation 2010
Long-term data of LAM in KTRs

Figure 5. Survival of HBsAg+ve kidney transplant recipients stratified according to lamivudine treatment. Patient survival was worst in those who underwent kidney transplantation prior to the availability of anti-viral therapy.

Figure 1. Relationship between the incidence of drug resistance and treatment duration in HBsAg+ve kidney transplant recipients treated with lamivudine.

- **a** = kidney transplantation before 1996 and treated with lamivudine, n=17
- **b** = kidney transplantation after 1996 and treated with lamivudine, n=21
- **c** = kidney transplantation before 1996 and not treated with lamivudine, n=25

High risk of LAM-resistance >60% after 5 years of Rx
Entecavir (ETV) in HBsAg+ KTR

Genotypic resistance ~20% with ↑HBV DNA and ALT after 20±3.5 months in LAM-resistant cases
Other NAs in HBsAg+ KTR

• Adefovir and Tenofovir:
  – nephrotoxic potential (e.g. 30-50% ADV-treated KTRs; some required discontinuation)

• Telbivudine
  – Promising anti-viral and renal profile

Fontaine H et al. Transplantation 2005
Tse KC et al. Clin Transplant 2010
Daude M et al. Transplantation 2011
Yap DY et al. Nephrology (Carlton) 2014
HCV & the Kidneys
HCV and the Kidneys

HCV predicts more rapid GFR (glomerular filtration rate) decline in CKD patients with diabetes.

HCV is associated with different types of glomerulonephritis (GN).

HCV prevalence is higher in patients with CKD than in the general population.

High HCV RNA
Genotype 2

Tsai TL, et al. Kidney Int 2017
Management of HCV-associated GN

• Depends on renal parameters & severe extra-renal complications

• Mild to mod UP, stable RFT
  – Anti-viral therapy (IFN/ribavirin/DAA)

• Nephrotic-range UP, progressive renal deterioration, presence of severe extra-renal manifestations (e.g. pulmonary hemorrhage)
  ➔Immunosuppressive Rx
  – CYC
  – Steroids
  – Anti-CD20
  – Plasmapheresis
  – Anti-viral therapy

Management of chronic HCV infection in renal failure patients
Milestones in Therapy of CHC: Average SVR Rates from Clinical Trials

SVR12 (HCV RNA neg 12wks after end of therapy) = cure

Adapted from US Food and Drug Administration, Antiviral Drugs Advisory Committee Meeting, April 27-28, 2011, Silver Spring MD.
Most DAAs Currently in Development Target One of Three Viral Proteins: NS3/4A, NS5A and NS5B

NS3/4A protease inhibitors
- Gilecaprevir (GLE)
- Asunaprevir (ASV)
- Boceprevir (BOC)
- Grazoprevir (GZV)
- GS-9857
- Paritaprevir (PTV)
- Simeprevir
- Sovaprevir
- Telaprevir
- Vedroprevir

NS5A inhibitors
- Pibrentasvir (PIB)
  - ACH-3102
  - BMS-824393
  - Daclatasvir (DCV)
  - Elbasvir
  - Velpatasvir (VEL)
  - GSK2336805
  - Ledipasvir (LDV)
  - Ombitasvir (OBV)
  - Samatasvir
  - MK-8408
  - Ravidasvir

NS5B polymerase inhibitors

Nucleoside
- MK-3682
- Sofosbuvir (SOF)

Non-nucleoside
- Beclabuvir
- PPI-383
- Dasabuvir (DSV)
- TMC647055

Abbvie
BMS
Gilead
Merck

Need at least ≥2 drugs of different classes for effective HCV regimen
#886, Vierling: RUBY-I: Safety and Efficacy of OBV/PTV/r + DSV ± RBV in GT1 Patients With Severe Renal Impairment or End-stage Renal Disease

**Severe renal impairment or ESRD, including dialysis ± cirrhosis, TN or IFN-TE**

- **GT1a/<F4** → Arm C
- **GT1a/F4** → Arm D
- **GT1b/F0–4** → Arm E

**Demographics, n (%)**

<table>
<thead>
<tr>
<th>Patients (N=48)</th>
<th>Black</th>
<th>Cirrhosis F4</th>
<th>Stage 4/5 CKD</th>
<th>Hemodialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>26 (54)</td>
<td>15 (31)</td>
<td>8 (17)/40 (83)</td>
<td>33 (69)</td>
<td></td>
</tr>
</tbody>
</table>

**Safety, n (%)**

<table>
<thead>
<tr>
<th>Patients (N=48)</th>
<th>Any AE</th>
<th>Anemia</th>
<th>SAEs</th>
<th>Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>41 (85)</td>
<td>19 (40)</td>
<td>13 (27)</td>
<td>2 (4)</td>
<td></td>
</tr>
</tbody>
</table>

**Anemia**

- Occurred only in patients receiving RBV
- Mild: n=11; moderate: n=6; severe: n=2
- 2 patients required interruption of study drugs
- Erythropoietin: n=7; transfusion: n=2

The data being presented may represent off-label data; please refer to your local country’s approved label for specific prescribing information for OBV/PTV/r + DSV ± RBV.
#935, Gane: RUBY-II: Efficacy and Safety of a **RBV-free** OBV/PTV/r ± DSV Regimen in GT1a and GT4 Patients With Severe Renal Impairment or End-stage Renal Disease

**End-stage renal disease (eGFR <30 mL/min), including hemodialysis**

Non-cirrhotic, TN

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Patients (N=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT1a/GT4</td>
<td>13 (72)/5 (28)</td>
</tr>
<tr>
<td>Dialysis</td>
<td>17 (94)</td>
</tr>
</tbody>
</table>

**Safety, n (%)**

<table>
<thead>
<tr>
<th></th>
<th>GT1a (n=13)</th>
<th>GT4 (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>13 (100)</td>
<td>5 (100)</td>
</tr>
<tr>
<td>SAEs</td>
<td>3 (23)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>AE leading to d/c</td>
<td>1 (8)*</td>
<td>1 (20)†</td>
</tr>
<tr>
<td>Hemoglobin, Grade ≥2 (&lt;10 g/dL)</td>
<td>4 (31)</td>
<td>2 (40)</td>
</tr>
<tr>
<td>ALT, Grade 3 (&gt;5–20 x ULN)</td>
<td>1 (8)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Total bilirubin, Grade ≥2 (&gt;1.5 x ULN)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Discontinued study drug but achieved SVR12
†Discontinued because of renal failure and transplant

The data being presented may represent off-label data; please refer to your local country’s approved label for specific prescribing information for OBV/PTV/r + DSV ± RBV
#LB-11, Gane: EXPEDITION-IV: Safety and Efficacy of Glecaprevir/ Pibrentasvir in Adults with Renal Impairment and Chronic HCV GT1–6 Infection

**GT1–6 ± compensated cirrhosis TN or TE (IFN- or SOF-based regimens) eGFR <30 mL/min/1.73 m²**

**Demographics**

<table>
<thead>
<tr>
<th>Demographics</th>
<th>N=104</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-experienced, IFN / SOF, n (%)</td>
<td>42 (40) / 2 (2)</td>
</tr>
<tr>
<td>Compensated cirrhosis, n (%)</td>
<td>20 (19)</td>
</tr>
<tr>
<td>HCV genotype, n (%)</td>
<td></td>
</tr>
<tr>
<td>GT1a / GT1b / GT1 other</td>
<td>23 (22) / 29 (28) / 2 (2)</td>
</tr>
<tr>
<td>GT2</td>
<td>17 (16)</td>
</tr>
<tr>
<td>GT3</td>
<td>11 (11)</td>
</tr>
<tr>
<td>GT4 / GT5 / GT6</td>
<td>20 (19) / 1 (1) / 1 (1)</td>
</tr>
<tr>
<td>CKD stage 4 / 5, n (%)</td>
<td>13 (12) / 91 (88)</td>
</tr>
<tr>
<td>eGFR &lt;15 mL/min/1.73 m², n (%)</td>
<td>86 (83)</td>
</tr>
<tr>
<td>Dialysis, n (%)</td>
<td>85 (82)</td>
</tr>
</tbody>
</table>

**SVR12 (%)**

<table>
<thead>
<tr>
<th>SVR12 (%)</th>
<th>N</th>
<th>ITT</th>
</tr>
</thead>
<tbody>
<tr>
<td>98</td>
<td>104</td>
<td>102</td>
</tr>
</tbody>
</table>

**Breakthrough** 0  
**Relapse** 0  
**Discontinuation** 1  
**LTFU** 1  

mITT - 100% SVR12; No virologic failures
HEV & the Kidneys
Chronic HEV infection in kidney transplantation recipients

- HEV infection usually acute & self-limiting

- HEV infection in solid organ transplant recipients
  ➔ chronic hepatitis (66%); cirrhosis (~10%)
  Most data reported: genotype 3

Management:

Ribavirin monotherapy (genotype 3)
HEV clearance (95%); recurrence (18.9%); SVR (75%)
Main S/E: anemia

Kamar N et al. Gastroenterology 2011
Chronic HEV infection in kidney transplantation recipients – Local Situation

- 4 patients HEV IgM + out of 446 kidney transplant recipients (prevalence ~ 0.9%)
- Three progressed to chronic HEV infection (all genotype 4)
- Two showed good response to ribavirin
- One with poor response (K1383N mutation identified in the RdRp gene)
Hepatorenal Syndrome (HRS)
Hepatorenal syndrome (HRS)

- Occurs in 10-20% patients with advanced cirrhosis
- High mortality without liver transplantation

Type 1 HRS:
- Rapid deterioration in renal function (doubling within 2 wks)
- Mortality 80% in 2 weeks

Type 2 HRS:
- Progressive course with moderate SCr to (133 mol/L)
- Associated with ascites & refractory to diuretics
- Median survival 4-6 months

Salerno F et al. Gut 2007
Renal impairment in advanced cirrhotic patients

Renal dysfunction on the background of cirrhosis

- Chronic kidney disease independent of underlying cirrhosis or associated with it
- Associated with circulatory dysfunction in cirrhosis

Hypovolemia
- Good response to fluids
- Tubular markers of renal injury are usually absent
- The kidneys are histologically normal

Hepatorenal syndrome
- Moderate response to terlipressin/albumin
- Tubular markers of renal injury may be present
- The kidneys are likely to be histologically normal

Associated with infection/inflammation and possible kidney injury
- Poor response to terlipressin/albumin
- Tubular markers of renal injury are highly likely to be present
- The kidneys are likely to be histologically abnormal

<table>
<thead>
<tr>
<th></th>
<th>Hypovolemia</th>
<th>HRS</th>
<th>ATN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary Na</td>
<td>&lt;20 mmol/L</td>
<td>&lt;10 mmol/L</td>
<td>&gt;40 mmol/L</td>
</tr>
<tr>
<td>Urine/plasma Cr</td>
<td>&gt;40:1</td>
<td>&gt;40:1</td>
<td>&lt;20:1</td>
</tr>
<tr>
<td>Urine/plasma osmolarity</td>
<td>&gt;1.2</td>
<td>&gt;1.2</td>
<td>1.0±0.1</td>
</tr>
<tr>
<td>Urinary sediment</td>
<td>normal</td>
<td>Normal</td>
<td>Granular casts</td>
</tr>
</tbody>
</table>

Pathophysiology of HRS

Conventional Belief:
• Vasomotor dysfunction

Novel Insights (Non-vasomotor mechanisms):
• Upregulation of inflammatory mediators
• TLR4
• IL-17A
• Biliary Cast nephropathy
• ↑Intra-abdominal pressure

Management of HRS

• Prevention of HRS is very important
  – Prevent precipitating factors (e.g. over-diuresis/paracentesis; infection; GIB)
  – Avoid nephrotoxic agents (e.g. contrast, NSAIDs)

• Definitive treatment: Liver transplantation

• Bridging therapy
  – Cautious volume expansion
  – Terlipressin + albumin
  – Other vasoactive drugs: midodrine, octreotide, pentoxyfylline
  – Dialysis (CVVH)
  – TIPS in exceptional cases
Diagnosis & Prediction of HRS

• Development of HRS:
  – often unpredictable & patients commonly deteriorate rapidly once HRS sets in
  – Serum creatinine (Cr) remains the conventional indicator of renal function.

• Interpretation of SCr in advanced cirrhotic patients confounded by:
  – Malnutrition and reduced muscle mass
  – Abnormal fluid distribution
  – Hyperbilirubinemia

• Serum Cr abnormality occurs late & relying on serum Cr alone or Cr-based equations results in delayed diagnosis and management of HRS.
Novel biomarkers in HRS diagnosis


<table>
<thead>
<tr>
<th>Tubular injury markers</th>
<th>PRA N=55</th>
<th>HRS N=16</th>
<th>ATN N=39</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGAL (ng/ml)</td>
<td>54 (17–180)</td>
<td>115 (51–373)</td>
<td>565 (76–1000) ***, ##</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IL-18 (pg/ml)</td>
<td>15 (15–49)</td>
<td>37 (15–90)</td>
<td>124 (15–325) ***, #</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>KIM-1 (ng/ml)</td>
<td>4.4 (1.8–11.7)</td>
<td>7.6 (4.5–10.1)</td>
<td>8.4 (4.1–18.3) **</td>
<td>0.03</td>
</tr>
<tr>
<td>L-FABP (ng/ml)</td>
<td>9 (4–18)</td>
<td>14 (6–20)</td>
<td>27 (8–103) ***</td>
<td>0.002</td>
</tr>
</tbody>
</table>

| Tubular function marker |          |         |          |         |
| FENa (%)                | 0.27 (0.13–0.58) | 0.10 (0.02–0.23) ** | 0.31 (0.12–0.65) ### | 0.01    |

| Glomerular injury marker |          |         |          |         |
| Albumin (mg/dL)         | 21 (4–70) | 24 (13–129) | 92 (44–253) ***, # | <0.001  |

<table>
<thead>
<tr>
<th>Tubular injury markers</th>
<th>Optimal Cut Point</th>
<th>Proportion Over Cut Point with ATN</th>
<th>AUC (95% CI)</th>
<th>Validation AUC*</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGAL (ng/ml)</td>
<td>365</td>
<td>25/35 (71%)</td>
<td>0.78 (0.69–0.88)</td>
<td>0.787</td>
</tr>
<tr>
<td>IL-18 (pg/ml)</td>
<td>85</td>
<td>21/33 (64%)</td>
<td>0.71 (0.61–0.81)</td>
<td>0.711</td>
</tr>
<tr>
<td>KIM-1 (ng/ml)</td>
<td>15.4</td>
<td>15/24 (63%)</td>
<td>0.64 (0.53–0.75)</td>
<td>0.639</td>
</tr>
<tr>
<td>L-FABP (ng/ml)</td>
<td>25</td>
<td>21/30 (70%)</td>
<td>0.69 (0.57–0.80)</td>
<td>0.688</td>
</tr>
</tbody>
</table>

| Tubular function marker   |          |         |          |         |
| FENa (%)                 | 0.1      | 22/62 (35%) | 0.56 (0.45–0.68) | 0.563 |

| Glomerular injury marker |          |         |          |         |
| Albumin (mg/dL)         | 44       | 29/52 (56%) | 0.73 (0.64–0.83) | 0.734 |
Biomarkers which predict HRS in cirrhotic patients with normal SCr

<table>
<thead>
<tr>
<th></th>
<th>Cut-off value</th>
<th>AUC</th>
<th>95% CI</th>
<th>PPV</th>
<th>NPV</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline urine NGAL</td>
<td>18.72 ng/mL</td>
<td>0.84</td>
<td>0.672</td>
<td>1.000</td>
<td>66.7%</td>
<td>91.3%</td>
</tr>
<tr>
<td>Baseline urine KIM-1</td>
<td>1.499 ng/mL</td>
<td>0.78</td>
<td>0.607</td>
<td>0.963</td>
<td>75.0%</td>
<td>84.2%</td>
</tr>
</tbody>
</table>

Incorporating these biomarkers into MELD score might better prioritize liver allograft?

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Either urinary NGAL or urinary KIM-1 above cut-off</td>
<td>5.600</td>
<td>1.780-17.621</td>
<td>0.001</td>
</tr>
<tr>
<td>Both urinary NGAL and urinary KIM-1 above cut-off</td>
<td>6.125</td>
<td>2.611-14.369</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Yap DY et al. Dig Liver Dis 2017
Questions

THANK YOU