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 GN

Chronic HBV Carrier

- HBeAg - IgG
  - MN
  - Type I MPGN

- HBsAg - IgG
  - PAN
  - Type I MPGN

- Type III MC

- Direct Tissue Infection
  - IgA, FSGS
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

References:

- 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

References:
- 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

- 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)
  \[\text{Immunosuppressive Rx}\]
  - 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**
  - Glecaprevir (GLE)
  - Asunaprevir (ASV)
  - Boceprevir (BOC)
  - Grazoprevir (GZV)
  - GS-9857
  - Paritaprevir (PTV)
  - Simeprevir
  - Sovaprevir
  - Telaprevir
  - Vedroprevir

- **NS5A inhibitors**
  - ACH-3102
  - BMS-824393
  - Daclatasvir (DCV)
  - Elbasvir
  - Velpatasvir (VEL)
  - GSK2336805
  - 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 $\geq 2$ 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

### Demographics, n (%)

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

### Safety, n (%)

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

Time (weeks)

GLE/PIB 300/120 mg QD (N=104)

<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 (%)

Phases 1–3 Single-arm Open-label

SVR12 (%)

Breakthrough 0
Relapse 0
Discontinuation 1
LTFU 1

mITT - 100% SVR; 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
  - Hypovolemia
    - Good response to fluids
    - Tubular markers of renal injury are usually absent
    - The kidneys are histologically normal
  - Hepatorenal syndrome
    - Moderate response to terlipressin/albunin
    - Tubular markers of renal injury may be present
    - The kidneys are likely to be histologically normal
  - Associated with circulatory dysfunction in cirrhosis
    - Associated with infection/inflammation and possible kidney injury
      - Poor response to terlipressin/albunin
      - 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></th>
<th>PRA N=55</th>
<th>HRS N=16</th>
<th>ATN N=39</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tubular injury markers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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>
<tr>
<td><strong>Tubular function marker</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FENa (%)</td>
<td>0.27 (0.13–0.58)</td>
<td>0.10 (0.02–0.23)**</td>
<td>0.31 (0.12–0.65)##</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Glomerular injury marker</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin (mg/dL)</td>
<td>21 (4–70)</td>
<td>24 (13–129)</td>
<td>92 (44–253)***, #</td>
<td>&lt;0.001</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th></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><strong>Tubular injury markers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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>
<tr>
<td><strong>Tubular function marker</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FENa (%)</td>
<td>0.1</td>
<td>22/62 (35%)</td>
<td>0.56 (0.45–0.68)</td>
<td>0.563</td>
</tr>
<tr>
<td><strong>Glomerular injury marker</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin (mg/dL)</td>
<td>44</td>
<td>29/52 (56%)</td>
<td>0.73 (0.64–0.83)</td>
<td>0.734</td>
</tr>
</tbody>
</table>
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>0.005</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>0.008</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</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</td>
<td>6.125</td>
<td>2.611-14.369</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Questions

THANK YOU