HCV – Treat now!

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Disclosures

- Dr Gish has advisory board relationships, consultancies, and speakers bureaus with Merck, Genentech, Roche, Gilead, BMS and AbbVie

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HCV current SVR/Cure rates

- **Genotype 1**
  - Triple PI PEG Based therapy: 70%+
  - Dual PEG therapy: 50-70%

- **Genotype 2**
  - Dual PEG based therapy: 80%+

- **Genotype 3**
  - Dual PEG based therapy: 70%+

- **Genotype 4**
  - Dual PEG based therapy: 50-70%
  - Triple PI PEG based therapy: >70% (Simeprevir)

- **Genotype 5**
  - TBD

- **Genotype 6**
  - PEG based therapies 50-70%
Aging of The HCV Population will Lead to a Peak of Cirrhosis in - 2020

Gary L. Davis, et al. gastroenterology 2010; 739-744
OVERVIEW

• Association between chronic HCV infection and:
  – Diabetes/insulin resistance
  – Cardiovascular disease
  – HCV and Brain
  – Cancer
  – Renal impairment

• Effects of antiviral therapy on prognosis:
  – Mixed cryoglobulinaemia
  – Liver-related mortality
  – Non-liver-related mortality
Chronic HCV Infection Affects Many Sites Beyond the Liver

- Neurological (e.g. cognitive impairment)
- Cardiovascular Diseases (CAD)
- Metabolic (e.g. diabetes)
- Autoimmune (e.g. cryoglobulinemic)
- Dermatological (e.g. porphyria cutanea tarda)
- Pulmonary fibrosis
- Renal (e.g. glomerulonephritis)
- Lymphoproliferative (e.g. B cell lymphoma)
Mechanism of Development of Extrahepatic Manifestations

• Immunological
  – Chronic persistence of virus leads to the circulation of immune complexes and autoimmune phenomenon
  – Mixed cryoglobulinemia (Ferri 207)

• Virological
  – Extrahepatic tropism of the virus
HCV Viremia Was Associated With Increased Mortality in a Prospective Taiwanese Cohort Study

Anti-HCV seronegative (n=18,541); anti-HCV seropositive (n=1095; detectable HCV RNA: 69.4%). Average follow-up: 16.2 years.
Among extrahepatic causes of death, 68.5% and 69.3% were noncancer deaths for HCV seronegative and seropositive, respectively.
*P<.001 for comparison among all 3 groups and P<.001 for HCV RNA detectable vs undetectable.
HCV and Renal disease

- HCV infection may lead to renal disease or be associated with renal disease
- Mixed cryoglobulinemia (type II cryoglobulins, or + RF)
- Membranoproliferative glomerulonephritis (MPGN)
- Polyarteritis nodosa

- Less common
  - Focal segmental glomerular sclerosis
  - Proliferative glomerulonephritis
  - Membranous GN
  - Fibrillary and immunotactoid glomerulopathies
HCV-related Renal Diseases

- Prevalence - 20-30% of patients have renal involvement
- 80% of them cryoglobulinemic (CG) MPGN
- ~ 50% of cases seen moderate urinary syndrome
- 25% develop severe acute nephritic syndrome
- 20% develop nephrotic syndrome

- For all states nephritis is characterized by severe hypertension.
- In one third of patients develop renal failure
HCV: Virologic Status of Renal Transplant Recipients

Graft and Recipient Survival

Graft Survival

Patient Survival

HCV infection is associated with lower graft and recipient survival

HOMA-IR and C-peptide Levels in Chronic HCV and HBV Infection

Association of Diabetes Mellitus (DM) and HCV Infection

- HCV was second strong predictor of DM2 after obesity.
- In patients with HCV infection DM2 occurred in more than 10 years younger population than in HCV-negative group.
- HCV infected patients who displayed any other risk factor for DM2 develop this condition 11 folder more likely compared with HCV-negative group.
- HCV is a trigger of DM2 in previously predisposed individuals.
Association of Diabetes Mellitus and HCV Infection
SVR Reduces Risk of Development of Diabetes in Patients with HCV

Veterans Affairs Clinical Case Registry: 27,636 patients with HCV Followed for median 5 years Antiviral treatment initiated 1998-2007

Hyder S. and et al Digestive Disease week, 2013

HR=0.77: 95% CL, 0.71-0.84

Patients with SVR (n=7617)
Patients without SVR (n=15,243)*
*Missing VL data n=4776
Mechanism Involved in the Diabetogenic Action of HCV

Th1 lymphocytes immune-mediated response → Hepatitis c virus infection → Liver fibrosis → Extracellular matrix → Insulin resistance → Type 2 diabetes mellitus → THF-a system activation → Liver fibrosis → liver steatosis → Hepatitis c virus infection → a interferons

Albert L. and et al
Diabetes Care, 2006
Cumulative Development Rate of HCC in HCV – Infected Patients Treated with IFN

- Retrospective cohort of 4302 Japanese patients treated with IFN-α followed for average 8.1 years.
- Cumulative incidence of HCC: 4.3% at 5 years, 10.5% at 10 years, 19.7% at 15 years.
- T2DM caused 1.73-fold increase in HCC.

HCC, hepatocellular carcinoma; IFN, interferon; SVR, sustained virological response; T2DM, type 2 diabetes.

Stroke Incidence and HCV Infection

4094 adults in Taiwan newly diagnosed with HCV infection compared with 16376 adults without HCV infection and matched by age and sex.
Carotid Atherosclerosis and Chronic HCV

Prevalence of carotid plaques according to age and fibrosis

- Age ≤55 years (F0-2): n=67
- Age ≤55 years (F3-4): n=21
- Age >55 years (F0-2): n=43
- Age >55 years (F3-2): n=43

p=0.008

p=0.51

F. fibrosis score

Peta S. and et al., Hepatology 2012.55.1317-1323
Cerebrovascular Deaths and HCV Infection

Community-based prospective cohort study: 23665 residents in Taiwan

- Cumulative risk (%)
  - Anti-HCV+ve: 2.7
  - Anti-HCV -ve: 1

- p<0.0001

- p<0.001 for trend
  - Anti-HCV+ve participants:
    - HCV RNA undetectable: 1.4
    - Low HCV RNA⁺: 2.36
    - High HCV RNA⁺: 2.82

Lee MH and et al. Stroke 2010
Increased Prevalence of Psychiatric Comorbidity in HCV – Infected Populations

Hashem B. El-Serag and et al. Gastroenterology 2002
HCV is Strongly Associated with Depression

Cellular Localization Of HCV Within The CNS: Microglia And Astrocytes

83 -95% of HCV NS3+ cells co-stained for CD68+ (microglia)

4-29 % of NS3+ cells co-stained for GFAP + (astrocytes)

Positive –and negative-strand HCV RNA detected in laser capture microdissected microglia (genomic equiv/400-650 cells)

HCV Infects the Endothelial Cells of the Blood-Brain Barrier

Two brain microvascular endothelial cell lines, hCMEC/D3 and HBMEC, express all the HCV entry factors

Fletcher NF and et al Gastroentology 2012
HCV Brain Syndrome: Mechanisms

Psychosocial effects

CNS effect of peripheral immune response?

“HCV Brain Syndrome”
Fatigue, Depression, Cognitive impairment

HCV infection of the CNS?
Association Between HCV, HBV and Breast Cancer Risk in Taiwan

Patients newly diagnosed breast cancer (n=1958) Age-matched cohort without cancer (n=7382)

Fu-Hsiung Su and et al. BML Cancer 2011
Pathogenesis of HCV-associated B-NHL

- **HCV** and **E2** activate B cells leading to **CB81**.
- **Polyclonal RF** and **Oligo and Monoclonal RF** are generated.
- **t(14;18) translocation** and **Bcl-2 activation**.
- **Gen mutation** (C-myc и etc.)
- **Mixt Cryoglobulinemia III type**
- **Mixt Cryoglobulinemia III-II и II type**
- **B-NHL (5-10%)**

Non-investigated genetic and environmental factors

Ignatova T.M; Hepatological Forum 2005/3
Chronic HCV Increases Mortality from Hepatic and Non-hepatic Diseases

The REVEAL HCV Cohort Study

23820 adults, Taiwan

1095 anti-HCV positive; 69.4% with detectable HCV RNA

HCV seropositive HCV RNA detectable
HCV seropositive HCV RNA undetectable
HCV seronegative

Cumulative mortality, (%)

Hepatic diseases

Extrahepatic diseases

Follow-up (years)

Cumulative mortality, (%)

The Management of Extrahepatic Manifestations in Patients with Chronic HCV - Infection

<table>
<thead>
<tr>
<th>Antiviral treatment</th>
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<tbody>
<tr>
<td>- Vasculitis: skin, lung, intestines, cerebral</td>
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<tr>
<td>- Raynaud's syndrome,</td>
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<td>- Polyneuropathy</td>
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<td>- Chronic glomerulonephritis</td>
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<td>- Lymphoproliferative diseases</td>
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<td>- Low-grade NHL</td>
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<td>- Myocarditis-</td>
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<td>- Granulomatosis of Lungs</td>
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<td>- Sjogren's syndrome-</td>
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<td>- Tubulointerstitial nephritis</td>
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<td>- with severe renal impairment</td>
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<td>- Autoimmune hemolytic anemia</td>
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<td>- Autoimmune thrombocytopenia</td>
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Therapy algorithm for HCV extrahepatic manifestations

Severity of disease

Primarily antiviral therapy*: PEG-IFN α+ribavirin

Responders

Follow-up

Non-responders or PEG-IFN α and/or ribavirin-induced aggravation

Corticosteroids +/- symptomatic therapy or early administration of rituximab

Primarily immunosuppressive therapy: corticosteroids +/- Cyclophosphamide +/- Plasmapheresis, alternatively rituximab

Responders

Non-responders or PEG-IFN α and/or ribavirin-induced aggravation

2nd antiviral therapy: PEG-IFN α+ RBV

Individual strategy +/- REG-IFN / ribavini

Modified from Craxi 2008
SVR Was Associated With Improved Long-Term Liver-Related Outcomes in the HALT-C Trial Database

Analysis of liver outcomes (decompensation, HCC, or death) in the HALT-C trial database. All comparisons $P<.0001$.

*Detectable HCV RNA at treatment week 20 (combination therapy was discontinued at week 24).

HALT-C=Hepatitis C Antiviral Long-Term Treatment against Cirrhosis.

SVR was associated with reduced long-term risk of all-cause mortality in an international, multicenter study.

International, multicenter, long-term follow-up study from 5 large tertiary care hospitals in Europe and Canada. Patients with chronic HCV infection started an interferon-based treatment regimen between 1990 and 2003 (n=530).

Conclusions

- Chronic HCV infection has adverse effects on many organ systems outside the liver.
- Some of these effects lead to significantly increased mortality.
- Improved antiviral efficacy might reduce morbidity and mortality from hepatic and non-hepatic causes.

Treat now!