Update on Hepatitis C and New Treatment Options

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HCV-GROWING HEALTH CONCERNS

- Since 2007 deaths from HCV have exceeded deaths from HIV
- HCV is four times as prevalent as HIV and HBV in the US
- Estimated 3.5-5.2 million persons with HCV in the US
  - 1.6 million have been diagnosed
  - 170,000 to 200,000 have been successfully treated
Hepatitis C—health concerns

- **Cirrhosis**
  - Estimated approximately 1 million patients in the United States will have cirrhosis secondary to hepatitis C by 2020.
  - Patients with cirrhosis are at risk of decompensation and liver failure, hepatocellular carcinoma

- **Extrahepatic manifestations**
  - Renal disease: nephritis, nephrotic syndrome
  - Vascular disease—cryoglobulinemia
  - Increased risk of non-GI malignancies:
    - Non-Hodgkins lymphoma, Prostate, thyroid and esophageal cancer
SCREENING FOR HCV-who to screen

- Any patient born between 1945 and 1965 “Baby Boomers”
- Transfusion of blood or blood products prior to 1992
- Hx of IVDU, snorting drugs, Tattoo’s, incarceration
- Dialysis patients-long term dialysis - screen every 6 months
- Abnormal liver enzymes ALT/AST greater than 19 for females, 30 for males
- Family history: low risk of maternal-fetal or sexual transmission
Initial Testing

- Hepatitis C antibody
  - Positive antibody ≠ Chronic hepatitis C - Further testing required
  - ≈ 20% false positive or spontaneous clearance

- Hepatitis C viral load-Quantasure or Quantasure plus
  - Any level of viremia confirms chronic Hepatitis C
  - Level of viremia does not correlate with extent of disease!
  - Qualitative tests
Positive viremia-now what?

- Additional workup required:
  - CBC, CMP, PT/Inr, HIV, Hepatitis A and B serologies,
  - Rheumatoid factor, Urinalysis, AFP
  - Ultrasound-complete with portal vein and spleen size
  - Genotype
  - Determination of fibrosis
Genotypes

- 6 major genotypes-numbered 1-6
- \( \approx 50 \) subtypes
- Genotype 1 most common in US followed by Geno 2, 3, rarely 4
- Genotype 3 is associated with significant fatty liver changes, more aggressive with increased risk of cirrhosis and Hepatocellular carcinoma-Hardest to treat
FIBROSIS

- Fibrosis is rated on a scale of 0-4 based on Metavir scoring
  - F0 = no fibrosis
  - F4 = Cirrhosis
- Serological tests:
  - Fibrosure, Fibrotest, Fibrometer
- Imaging:
  - Fibroscan, MRI elastography
- Liver biopsy
CIRRHOSIS

- Patients with cirrhosis need further evaluation to determine if they are compensated or decompensated
  - Child-Pugh score
    - Hepatic encephalopathy
    - Ascites
    - Total bilirubin
    - Serum albumin
    - PT/INR

Hepatoma surveillance

- Ultrasound every 6 months for patients with stage III or stage IV fibrosis
- Indefinitely even if the hepatitis C is eradicated
- Alpha-fetoprotein is used by some centers although results can be confusing.
Cirrhosis—continued

- Patients with cirrhosis need evaluation for portal hypertension
  - Screening for esophageal varices
- Decompensated cirrhotics-Childs B or C need tertiary referral
  - Possible referral to transplant center
  - Risk of worsening decompensation/death with some of the new treatment options
- MELD score—predictive of mortality
  - Based on creatinine, total bilirubin and INR
  - Meld 15 or greater needs referral, possible evaluation for transplant
Selection for treatment

- Updated recommendations from AASLD/IDSA is at all patient should be considered for treatment
  - Exception: Patients with short life expectancy, <1 year
TREATMENT

≈20 YEARS-INTERFERON BASED TREATMENT

- Interferon
- Interferon/ribavirin
- Pegylated interferon/ribavirin

Numerous side effects—poor tolerability
Serious adverse events
Overall success rate ≈40%
DIRECT ACTING ANTIVIRALS-DAAs

- First generation: Protease inhibitors
  - Boceprivir
  - Telaprivir

  Used with Peg/rib for Genotype 1 only
  - Shorter duration-24 versus 48 weeks
  - ~70% response rate
  - Additive side effects-anemia, rash
  - No longer used
DAAs (cont)

- Simeprivir-Protease inhibitor
- Sofosbuvir-NS5B NUC inhibitor
  - Initially used with PEG/Rib
  - 12 week duration
  - ~90% response rate
  - Better tolerated-little additive side effects
- Sim/Sof combo first non-interferon treatment option
DIRECT ACTING ANTIVIRALS-Today
Multiple classes-multiple combinations*
Overall response rate < 95%

- RIBAVIRIN 5’UTR
- NS3 PROTEASE INHIBITORS
  - Simeprevir
  - Paritaprevir
  - Grazoprevir
- NS5A inhibitors
  - Daclatasvir
  - Ledipasvir
  - Ombitasvir
  - Elbasvir
- NS5B NUC INHIBITORS
  - Sofosbuvir
- NS5B non-NUC INHIBITORS
  - Dasabuvir

*Note-no single agent therapy is approved-combination therapy must be used
COMBINATION TREATMENTS

- Many of the new DAAs are provided as two or more medications combined in a fixed dose
- Harvoni- Ledipasvir/sofosbuvir
- Viekira pak-Ombitasvir/paritaprevir/ritonavir* plus dasabuvir
- Zepatier-elbasvir/grazoprevir
- Technivie-ombitasvir/paritaprevir/ritonavir*

*not a DAA-potentiates paritaprevir
SELECTION OF TREATMENT REGIMENS

- Choice of regimen, treatment duration, and use of ribavirin depends on:
  - Presence of cirrhosis
    - Protease inhibitors are not approved for decompensated cirrhosis-risk of worsening liver status-death
  - Prior treatment experience
    - PEG/Rib failure
    - Prior protease inhibitor failure
    - Prior sofosbuvir failure
  - Genotype
    - 1a versus 1b
    - 2-6
AASLD/IDSA guidance document

Dynamic document, up-to-date on all treatment options

Currently ~40 treatment options plus 15 options Not recommended
DRUG INTERACTIONS

- POTENTIAL DRUG-DRUG INTERACTIONS VARY BY DAA AND TREATMENT COMBINATIONS:
  - Need complete medication history including Herbal meds and supplements, e.g. St John’s Wort
  - Interactions may increase or decrease effectiveness of co-medication or DAA
  - Co-medications may require dose adjustment or may be contraindicated
  - Serious adverse events have been reported: e.g. Amiodorone and Sofosbuvir
  - Use on-line drug interaction websites and/or pharmacy consultation
  - Caution patients about starting any new meds while on treatment
TREATMENT AUTHORIZATION

- Access to treatment varies by region and payer despite AASLD recommendations that all patients should be treated.
- Many payers are still restricting treatment to patients with advanced fibrosis F3-F4, some will approve females of childbearing age.
- Specific pre-treatment testing such as drug screen may be required.
- Specialty pharmacies are often required and can be helpful with obtaining authorization and appeals. E.g. Acaria, Avella, Diplomat.
- Issues can arise when patients change or loose coverage while on treatment.
ON TREATMENT MONITORING-SIDE EFFECTS

- Overall side effects from the new DAAs tend to be mild and meds are well tolerated. Common side effects include mild headache, fatigue, sleeping difficulties, nausea and mild diarrhea. Certain DAAs may cause temporary elevations of ALT or bilirubin-follow medication prescribing guidelines

- Ribavirin
  - Many treatment protocols still require use of ribavirin
  - Ribavirin has been shown to be teratogenic and is strictly contraindicated with pregnancy
  - Patients or spouses of patients on Ribavirin must be on two strict forms of contraception during treatment and for six months after discontinuing ribavirin and have a negative pregnancy test prior to starting treatment and monthly pregnancy test during treatment and for six months after
  - Certain DAAs may interact with contraceptives rendering them ineffective
Due to the high efficacy and safety of the new DAAs routine testing on treatment for non-cirrhotics may not be required, However most insurers require a week four viral load to ensure the patient is compliant and is responding-if low level viremia is present I recommend retesting 2 week later

- Patients on Ribavirin may need periodic testing for anemia
- Zepatier guidelines recommend liver tests at 8 weeks of treatment as well as baseline NS5A resistance testing for Geno 1a patients prior to treatment
- A quantitative viral level should be done 12 weeks post treatment

  Undetectable viral load at 12 weeks post treatment indicates a sustained virological response (SVR) and is considered a “Cure”

  Note-successful treatment does not provide immunity from re-infection!
FUTURE TREATMENTS

- New combination treatments
- Novel mechanisms of action
- Pan-genotypic?
- Shorter treatment duration
- Less cost?
- Options for prior DAA treatment failures
CONCLUSION

- Hepatitis C continues to present a rapidly growing burden on our health care system for the foreseeable future
- We must identify affected patients and offer treatment to all those eligible
- Burden of treatment for non-complicated patients is expected to shift to primary care
- Treatment options exist for nearly every patient including patients with advanced liver disease-Childs B or C, renal patients and HIV co-infected
- Additional treatment options are on the horizon