A Revolution in Medicine: Advances in the Treatment of Hepatitis C Infection

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• At the end of the presentation, pharmacist participants will be able to:
  – Identify the primary differences between hepatitis A, B, and C
  – Review traditional treatment options for hepatitis C and describe why these treatment options are problematic for patients
  – Discuss new pharmacotherapy options for treatment of hepatitis C infection
  – Describe which treatment options are appropriate for the individual genotypes of hepatitis C
  – Select the most appropriate hepatitis C therapy for different patient cases
Objectives

• At the end of the presentation, pharmacy technician participants will be able to:
  – Describe the basic differences between hepatitis A, B, and C
  – Name the new treatment options for the various genotypes of hepatitis C
• **Viral hepatitis**
  - Major cause of morbidity and mortality worldwide
  - Hepatitis A, B, and C are most common
  - Chronic hepatitis is 3-5 times more common than HIV infection
  - Risks for infection and treatment options differ widely between hepatitis A, B, and C
  - Lack of knowledge is common for both healthcare workers and the general population
Hepatitis A

- Transmission occurs via fecal-oral route
- Typically associated with foreign travel
- Infection is acute but self-limited
  - Most recover by 2 months, but no later than 6 months
  - Does not progress to chronic infection
  - Rarely causes liver failure
- Treatment is strictly supportive care
  - Antiviral therapy is not indicated
- Vaccine available
Hepatitis B

• Transmission via parenteral, perinatal, or sexual exposure
• Can cause both acute and chronic infection
• Several drug therapies available, although resistance is increasing
• Not currently curable
  – Much research is underway
• Immunization is key to prevention
Hepatitis C

- Hepatitis C Virus (HCV)
  - Most common blood-borne pathogen in the United States
    - 4 million infected in the US
    - 180 million worldwide
  - Primary cause of:
    - Liver disease and
    - Liver-related deaths
  - Most common reason for liver transplantation
Hepatitis C

- Single-stranded RNA virus belonging to the family Flaviviridae of the genus *Hepacivirus*
- Initial infections begins with an acute phase, which usually progresses to a chronic infection
- ~25% of patients eradicate infections during the acute phase
  - The remainder progress to chronic infection
Hepatitis C

• Genotypes
  – Seven different genotypes, numbered 1-7
    • Each has multiple subtypes categorized “a, b, c,...”
    • Example: 1a, 2b, etc.

• Genotype 1 is most common in US
  – ~70-75% of infections

• Genotype 2
  – ~20% of infections
• Signs and Symptoms
• Acute
  – Nonspecific, often asymptomatic
  – Nausea/vomiting/diarrhea
  – Jaundice
• Chronic
  – Fatigue, loss of appetite
  – Jaundice
  – Spider angioma
Hepatitis C

- Transmission
  - Blood-borne virus
    - Injection drug use
    - Blood transfusions
    - Perinatal
    - Sexual contact
      - Only if blood exposure occurs
    - Unsterilized needles
      - Tattooing
      - Acupuncture
Hepatitis C Screening

- Injection drug users
- HIV or HepB infection
- Blood transfusions or solid organ transplantation prior to 1992
- Receipt of clotting factors prior to 1987
- Receiving hemodialysis
- Unknown cause of increased ALT
Hepatitis C Screening

- Children of HCV-infected mothers
- Sexual partners of HCV-infected patients
- Use of unsterilized needles
  - Tattooing
  - Acupuncture
  - Body piercing
- All individuals born between 1945 and 1965 should receive a one-time screen
  - Regardless of risk factors
Goals of Treatment

• Decrease all-cause mortality
• Decrease liver-related adverse health effects
  – End-stage liver disease
  – Hepatocellular carcinoma
• Virologic cure defined as a maintenance of a sustained virologic response (SVR)
  – Undetectable HCV RNA using a highly sensitive assay
Hepatitis C Treatment

- Treatment recommended for ALL patients with chronic HCV infection
- EXCEPTIONS:
  - Short life expectancies that cannot be helped though:
    - HCV treatment
    - Liver transplantation
    - Other medical treatments
Treatment

• Definition of cure:
  – SVR at 24 weeks following the completion of therapy

• Quantitative HCV viral load should be conducted at week 4 following start of treatment
  – Repeat at 12 weeks (end of treatment)

• If detectable at week 4, repeat at week 6
Pharmacotherapy

• Pegylated interferon-alpha (PEG-IFN) + ribavirin (RBV)
  – Standard of care for many years
  – Associated with poor SVR and many adverse effects

• Direct-acting antivirals (DAAs)
  – Several classes of new agents
  – Highly efficacious (>90%) with minimal adverse effects
• Mainstay of treatment prior to advent of DAAs
• Pegylated formulation allows for once weekly dosing
• ADRs make tolerability problematic
  – Fever
  – Weight loss
  – Depression
  – Neutropenia
Ribavirin

- Traditionally used in combination with PEG-INF
  - Still used occasionally in combination with DAAs
- Requires weight-based dosing
- Better tolerated than PEG-IFN, but ADRs still problematic
  - Dry cough
  - Pruritus
  - Hemolytic anemia
  - Teratogenic
Direct-Acting Antivirals

- **NS3-4 A Protease Inhibitors**
  - Simeprevir
  - Grazoprevir
  - Paritaprevir

- **NS5A Inhibitors**
  - Daclastavir
  - Ledipasvir
  - Ombitasvir
  - Elbasvir
  - Velpatasvir
Direct-Acting Antivirals

- NS5B Nucleoside Inhibitors
  - Sofosbuvir
- NS5B Non-Nucleoside Inhibitors
  - Dasabuvir
- DAAs have few ADRs and high tolerability compared to PEG-IFN and RBV
- Associated with HCV cure rates approaching 100%
Sofosbuvir

- Sovaldi®
- Used in combination with other DAAs
  - Available alone and as combined with several other drugs
- Can be used in combination for treatment of genotypes 1-6
- NOT to be used alone!!!
- Once daily dosing
Sofosbuvir

• Generally well-tolerated

• ADRs
  – Headache
  – Fatigue
  – Nausea

• Drug interactions
  – P-glycoprotein substrate
  – Amiodarone
Simeprevir

- Olysio®
- Used in combination with sofosbuvir for treatment of genotypes 1a and 1b
- Can also use in combination with PEG-INF + ribavirin
- NOT to be used alone!!!
- Once daily dosing
Simeprevir

• Must be taken with food
• ADRs
  – Photosensitivity
  – Bilirubin elevation
  – Nausea/vomiting
• CYP3A4 substrate
  – Must be cognizant of drug interactions for increased/decreased effect
  – Amiodarone
Daclatasvir

- Daklinza®
- Used primarily for treatment of genotype 3
  - Can be used as an alternative for genotypes 1 and 2
- Usually used in combination with sofosbuvir
  - NOT to be used alone!!!
- Once daily dosing without regard to food
- ADRs: headache, fatigue, nausea/vomiting
- Drug interactions: CYP3A inducers, amiodarone
  - Dosing adjustment may be required
Ledipasvir/sofosbuvir

• Harvoni®
• Used for treatment of genotypes 1, 4, 5, and 6
• Favorable ADR profile
  – Tiredness
  – Headache
  – Weakness
• 1 pill, once daily treatment
• Taken without regard to food
• Drug-interactions
  – P-glycoprotein inducers
    • St. John’s wort, rifampin
    • Decreased serum concentration of ledipasvir
  – PPIs/H2 antagonists
    • Decreased effect of ledipasvir
  – Rosuvastatin
    • Increased risk of rhabdomyolysis
  – Amiodarone
    • Symptomatic bradycardia
Elbasvir/Grazoprevir

- Zepatier®
- Used for the treatment of genotypes 1 and 4
- Useful in both treatment naïve patients and those with compensated cirrhosis
- Testing for resistance to NS5A inhibitors is recommended if treating genotype 1a
- One tablet once daily without regard to food
Elbasvir/Grazoprevir

• Contraindications:
  – Moderate/severe hepatic impairment (Child Pugh B or C)

• ADRs:
  – Fatigue
  – Headache
  – Nausea

• Drug interactions:
  – CYP3A substrate
• **Viekira Pak®**

• Combination of three DAAs
  – Ritonavir is used as a boosting agent for paritaprevir

• Ombitasvir/paritaprevir/ritonavir are combined into a tablet
  – 2 tablets in the morning with food

• Dasabuvir is administered twice daily
Ombitasvir/Paritaprevir/Ritonavir/Dasabuvir

- XR formulation now available
  - 3 tablets taken once daily with food
  - Likely better for patient compliance
- Useful in genotypes 1 and 4
- No renal dose adjustments required
- All formulations must be taken with food for increased absorption
Ombitasvir/Paritaprevir/Ritonavir/Dasabuvir

• Drug interactions
  – Paritaprevir/ritonavir primarily metabolized through CYP3A4
  – Major potential for drug interactions

• ADRs
  – Fatigue
  – Nausea/vomiting
  – Pruritus/skin reactions
  – Insomnia
Sofosbuvir/Velpatasvir

- Epclusa®
- First available drug active against HCV genotypes 1-6
- One pill once daily without regard to food
- Can also be used in combination with RBV for patients with decompensated cirrhosis
- Is usually now the preferred option for treating genotypes 2-6
Sofosbuvir/Velpatasvir

• Drug interactions
  – P-glycoprotein substrate
  – Velpatasvir is a substrate of several CYP enzyme systems
    • Avoid use with potent CYP inducers
  – Amiodarone

• ADRs
  – Generally well tolerated
  – Headache
  – Fatigue
Recommendations from the Treatment Guidelines
Genotype 1a & 1b

- Treatment–naïve, No cirrhosis
  - Elbasvir/grazoprevir
  - Ledipasvir/sofosbuvir
  - Paritaprevir/ritonavir/ombitasvir/dasabuvir
    - RBV must be added if treating genotype 1a
  - Sofosbuvir/velpatasvir
  - Simeprevir + Sofosbuvir
  - Daclatasvir + Sofosbuvir
    - Lower evidence

- Recommended duration is 12 weeks
Genotype 1a

- Treatment-naïve, compensated cirrhosis
  - Elbasvir/grazoprevir
  - Ledipasvir/sofosbuvir
  - Sofosbuvir/velpatasvir
- All have equal levels of evidence
- Recommended duration is 12 weeks
Genotype 1b

• Treatment-naïve, with compensated cirrhosis
  – Elbasvir/grazoprevir
  – Ledipasvir/sofosbuvir
  – Sofosbuvir/velpatasvir
  – Paritaprevir/ritonavir/ombitasvir/dasabuvir + ribavirin

• Recommended duration is 12 weeks
Genotype 2

- Treatment-naïve, without cirrhosis
  - Sofosbuvir/velpatasvir x 12 weeks
  - Daclatasvir + sofosbuvir x 12 weeks
    • Alternative; lower quality of evidence

- Treatment-naïve, compensated cirrhosis
  - Sofosbuvir/velpatasvir x 12 weeks
  - Daclatasvir + sofosbuvir x 16 to 24 weeks
    • Alternative; lower quality of evidence
Genotype 3

• Treatment-naïve, without cirrhosis
  – Sofosbuvir/velpatasvir x 12 weeks
  – Daclatasvir + sofosbuvir x 12 weeks

• Treatment-naïve, compensated cirrhosis
  – Sofosbuvir/velpatasvir x 12 weeks
  – Daclatasvir + sofosbuvir x 24 weeks
    • With or without ribavirin
    • Lower quality of evidence
Genotype 4

- Treatment-naïve, without cirrhosis **AND** with compensated cirrhosis
  - Sofosbuvir/velpatasvir
  - Paritaprevir/ritonavir/ombitasvir/dasabuvir + ribavirin
- Alternatives
  - Elbasvir/grazoprevir
  - Ledipasvir/sofosbuvir
- Recommended duration is 12 weeks
Genotypes 5 & 6

- Treatment-naïve, without cirrhosis **AND** with compensated cirrhosis
  - Preferred:
    - Sofosbuvir/velpatasvir
  - Alternative:
    - Ledipasvir/sofosbuvir
- Recommended duration of therapy is 12 weeks
Pharmacotherapy

• Things to consider when selecting a treatment:
  – Laboratory data
    • Baseline resistance
    • Cirrhosis
  – Patient compliance
    • Pill burden
  – Necessity of added RBV
  – Potential for drug interactions
  – Adverse effect profile
  – Cost/formulary issues
Case 1

• HPI: G.E. is a 60 year old male who presents to his PCP for an annual examination
• Allergies: NKDA
• PMH: HCV (diagnosed 2008), DM2, HTN, dyslipidemia
• Medications: HCTZ, lisinopril, metformin, rosvastatin
• PE: WNL
Case 1

- All of G.E.’s medical conditions are currently controlled with his medications.
- He has never been treated for his HCV, but his LFT’s have been steadily increasing.
- His PCP feels it is time to treat his HCV.
- Is it appropriate to treat G.E. at this time?
Case 1

• Which of the following would be the most appropriate recommendation for G.E. to treat his HCV? Assume he has genotype 1a and no baseline resistance.
  – A) Elbasvir/grazoprevir
  – B) Ledipasvir/sofosbuvir
  – C) Paritaprevir/ritonavir/ombitasvir/dasabuvir
  – D) Simeprevir + Sofosbuvir
Case 2

• What if G.E. had genotype 1b and compensated cirrhosis? What would be the best recommendation at this time?
  – A) Elbasvir/grazoprevir
  – B) Ledipasvir/sofosbuvir
  – C) Paritaprevir/ritonavir/ombitasvir/dasabuvir + ribavirin
  – D) Simeprevir + Sofosbuvir
Case 3

• What if G.E. had genotype 4?
• What if he was non-compliant with his other medications and his disease states were not controlled? Would this change your management?
• What laboratory parameters would you monitor?
QUESTIONS???
• SOVALDI [Package insert]. Foster City, California: Gilead Sciences; 2013.
• HARVONI [Package insert]. Foster City, California: Gilead Sciences; 2016.
• EPCLUSA [Package insert]. Foster City, California: Gilead Sciences; 2016.