Mevyret - A novel drug for chronic Hepatitis C

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ABSTRACT

Hepatitis C virus was discovered in 1989 and it was established as an important cause of chronic hepatitis since then. Lot of advances occurred in the field of management of viral hepatitis C. Intramuscular injection of peg alpha interferon was first approved drug for treatment in 2001, then came ribavirin. This combination was used for managing few genotypes of HC virus. Thereafter series of directly acting drugs (DAA) were progressively approved for one or other strains of HCV. **Mevyret is the recently approved, pan-genotypic HCV agent.** It is a novel double combination therapy that offers an all-oral, interferon-free, once-daily regimen for chronic hepatitis C. This update gives the pharmacology of this novel drug.

Key words : Chronic hepatitis C, Directly acting antivirals, Mevyret

Introduction

Chronic Hepatitis C (CHC) is an important viral infection of public health importance. Hepatitis C is caused by various genotypes (1-6) of the Hepatitis C virus (HCV). The infection may lead to chronic hepatitis, decompensated cirrhosis, and hepatocellular carcinoma, causing significant morbidity and mortality.[1]

Many advances occurred in the field of pharmacological management of Chronic hepatitis C. First ever drug approved for HC was pegylated alpha interferon an injectable drug, way back in 2001 followed by ribavirin. This combination was used for many years but SVR could not be achieved in significant percentage of patients. A better understanding of the lifecycle of HCV has lead to knowledge of several potential protein targets for the management. This in turn lead to the development of several potential direct-acting antiviral drugs (DAAs) targeting [NS3/4A protease inhibitors, NS5B nucleos(t)idic and non-nucleos(t)idic polymerase inhibitors, NS5A replication complex inhibitors[2] Oral combination of new DAAs has now became the standard of care for chronic HCV in treatment-naïve or treatment-experienced patients.

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Mevyret a combination of Glecaprevir and Pibrentasvir, is recent addition to the armatorium of the drugs in CHC. The approval is based on data from nine major clinical studies.: ENDURANCE-1,2,3,4, EXPEDITION-1&4 , SURVEYOR-1,2, and MAGELLAN-1. These trials showed overall SVR rates of 99% with 8 and 12 weeks of Mevyret. Mevyret also showed excellent efficacy in patients with the difficult-to-treat genotype 3 (SVR rates of 95-98%).

Mechanism of action : It is a combination of **Glecaprevir and Pibrentasvir.** These drugs are effective in combination as they have different targets of action. Glecaprevir is HCV NS3/4 protease inhibitor which is necessary for the proteolytic cleavage of the HCV-encoded polyprotein and is essential for viral replication. Glecaprevir binds to active site of HCV protease. Pibrentasvir on the other hand inhibits non-structural protein 5A (NS5A), limiting viral replication (direct-acting antiviral) and virion assembly. **Mevyret is effective against all genotypes of HC virus.**

Pharmacokinetic properties[3]

After oral ingestion absorption of both the drugs occur in 5 hours.

Half life of Glecaprevir is 6 hours and that of pibrentasvir is 13 hours.

Metabolism : for glecaprevir : liver partially; CYP450 : CYP3A4 substrate (partial); for pibrentasvir : none; CYP450 : none

Distribution : 97.5% of Glicaprevir and > 99.9% of Pibrentasvir remain bound to protein in blood.

Excretion : Major route of excretion for both drugs is biliary - fecal.

Dosage Forms & Strengths

Glecaprevir / pibrentasvir, available as tablet 100 mg / 40 mg.

Dose : 3 tablets (ie, 300 mg/120 mg total dose) PO once daily with food.

Indications[6,7]

1. Treatment-naïve adults with chronic hepatitis C virus (HCV) genotypes 1-6 without cirrhosis or with compensated cirrhosis (Child-Pugh A)
2. Treatment-experienced patients with HCV genotype 1 who have been previously treated with a regimen containing either an NS5A inhibitor or an NS3/4A protease inhibitor, but not both
3. Treatment experienced patients (previous treatment with peginteferon and ribavirin and/or Sovaldi, genotypes 1-6
4. Patients with chronic kidney disease (CKD) with HCV genotype 2, 3, 5 or 6 infection

Recommended duration for treatment-naïve patients

- Genotypes 1-6, no cirrhosis : 8 weeks (wk)
- Genotypes 1-6, compensated cirrhosis (Child-Pugh A) : 12 wk

Recommended duration for treatment-experienced patients[6]

- ***No cirrhosis***
  - Genotype 1 and NS5A inhibitor prior treatment : 16 wk
  - Genotype 1 and NS3/4A protease inhibitor prior treatment : 12 wk
  - Genotypes 1,2,4,5, or 6 (prior treatment with simeprevir and sofosbuvir, or simeprevir, boceprevir, or telaprevir with pegylated interferon and ribavirin) : 8 wk
  - Genotype 3 (prior treatment with simeprevir and sofosbuvir, or simeprevir, boceprevir, or telaprevir with pegylated interferon and ribavirin): 16 wk
- ***Compensated cirrhosis (Child-Pugh A)***
  - Genotype 1 and NS5A inhibitor prior treatment : 16 wk
  - Genotype 1 and NS3/4A protease inhibitor prior treatment: 12 wk
  - Genotypes 1, 2, 4, 5, or 6 (prior treatment with simeprevir and sofosbuvir, or simeprevir, boceprevir, or telaprevir with pegylated interferon and ribavirin) : 12 wk
  - Genotype 3 (prior treatment with simeprevir and sofosbuvir, or simeprevir, boceprevir, or telaprevir with pegylated interferon and ribavirin): 16 wk

Dosage Modifications

Renal impairment

- No dosage adjustment required in mild, moderate, or severe renal impairment including patients on dialysis

Hepatic impairment

- Mild (Child-Pugh A) : No dosage adjustment required
- Moderate (Child-Pugh B) : Not recommended
- Severe (Child-Pugh C) : Contraindicated

Adverse Effects

No major adverse event have been reported so far with Mevyret Minor adverse effects are headache, fatigue, nausea, diarrhea and increased bilirubin, $\geq$2x ULN.

Pregnancy

There are no adequate, well-controlled studies in pregnant women who have taken Mevyret. It should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation

The safety of breast feeding while taking Mevyret has not been established in humans. So one has to weigh potential benefits to mother and infant and possible risks in health and development of infant.

Warning

It is essential to rule out Hepatitis B co-infection, as reactivation of HB has been reported in these patients who are not receiving HBV antiviral

therapy. Hence prior to the initiation of treatment it is mandetory to measure HbsAg, and anti HBc for evidence of current or prior HBV infection. Fulminant hepatitis, hepatic failure, and death have been reported in HCV/HBV coinfection. Therefore it is essential to monitor HCV/HBV - coinfected patients for hepatitis flare or HBV reactivation during HCV treatment and posttreatment follow up Initiate appropriate patient management for HBV infection as clinically indicated

Contraindications

Severe hepatic impairment (Child-Pugh C)

Coadministration with atazanavir or rifampicin

Drug interactions

Coadministration is contraindicated with rifampin or atazanavir

Coadministration is not recommended with carbamazepine, efavirenz, or St John's wort

Conclusion

Mevyret is an effective oral combination drug which is highly effective in all genotypes of Hepatitis C virus, in patients without cirrhosis or with compensated cirrhosis, in patients with renal impairement and also patients with treatment failure

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