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Recommendation for treatment of hepatitis C virus infection

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I. INTRODUCTION

Treatment of hepatitis C virus (HCV) infection includes treatment-naïve patients and patients with treatment experience, either interferon, peginterferon plus ribavirin or any direct-acting antivirals (DAA). Recommended regimens are those that are favored for most chronic hepatitis C (CHC) patients in a given group, based on optimal efficacy, favored tolerability and adverse effect profiles and duration. Alternative regimens are also effective but relative to recommended regimes because of having potential disadvantages, limitations for use in such populations, or less supporting data than recommended regimens.

The following treatment regimens are listed in order of level of evidence. Some were reimbursed in Turkey. According to unpublished data, until today, in Turkey, sustained virological response (SVR) rate of either a combination of ledipasvir/sofosbuvir or a combination of paritaprevir/ritonavir/ombitasvir with dasabuvir with/without ribavirin is more than 90% in CHC patients with/without cirrhosis.

II. TREATMENT FOR PATIENTS INFECTED WITH GENOTYPE 1

II.A. Treatment for Patients Infected with Genotype 1 (G1)

There are several DAA regimes are recommended for treatment-naïve patients infected with genotype 1. The recommended regimens were changed based on the HCV subtype, baseline NS5A status and the presence or absence of compensated cirrhosis were effect on. CHC patients infected with genotype 1a may have a higher virological failure rates in comparison with genotype 1b infection.

II. HCV Treatment in G1 Patients

There are several recommended regimens with comparable efficacy. Some were on market in Turkey*.

II.A. Treatment in G1a Patients

II.A.1 Treatment-Naive G1a Patients

II.A.1.a Treatment for Patients without Cirrhosis

- A combination of ledipasvir (90 mg/d)/sofosbuvir (400 mg/d) for 12 weeks*.
  - Daily fixed dose combination of ledipasvir (90 mg/d)/sofosbuvir (400 mg/d) for Eight weeks in patients, whose HCV RNA level is <6 million IU/mL
- A combination of paritaprevir (150 mg/d)/ritonavir (100 mg/d)/ombitasvir (25 mg/d) with dasabuvir (500 mg/d) plus weight-based ribavirin for 12 weeks*.
- A combination of daclatasvir (60 mg/d)/sofosbuvir (400 mg/d) for 12 weeks*
- A combination of sofosbuvir (400 mg/d)/velpatasvir (100 mg/d) for 12 weeks

Alternative Regimens

- A combination of elbasvir (50 mg/d)/grazoprevir (100 mg/d) for 12 weeks if no baseline NS5A Resistance-associated substitutions (RAS) for elbasvir.
- A combination of simeprevir (150 mg/d)/sofosbuvir (400 mg/d) for 12 weeks if there were no basal Q80K mutations*

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II.A.1.b Treatment for Patients with Compensated Cirrhosis

- A combination of ledipasvir (90 mg/d)/sofosbuvir (400 mg/d) for 12 weeks*
- A combination of paritaprevir (150 mg/d)/ritonavir (100 mg/d)/ombitasvir (25 mg/d) with dasabuvir (500 mg/d) plus weight-based ribavirin for 24 weeks*
- A combination of daclatasvir (60 mg/d)/sofosbuvir (400 mg/d) plus weight-based ribavirin for 12 weeks or without ribavirin for 24 weeks*
- A combination of sofosbuvir (400 mg/d)/velpatasvir (100 mg/d) for 12 weeks

Alternative Regimens

- A combination of elbasvir (50 mg/d)/grazoprevir (100 mg/d) for 12 weeks if no baseline NS5A RAS for elbasvir.
- A combination of simeprevir (150 mg/d)/sofosbuvir (400 mg/d) for 24 weeks if there were no basal Q80K mutations*

II.A.2. Treatment For G1a patients with Peginterferon/Ribavirin-Experienced

II.A.2.a. Treatment for Patients without Cirrhosis

- A combination of ledipasvir (90 mg/d)/sofosbuvir (400 mg/d) for 12 weeks*.
- A combination of paritaprevir (150 mg/d)/ritonavir (100 mg/d)/ombitasvir (25 mg/d) with dasabuvir (500 mg/d) plus weight-based ribavirin for 12 weeks*.
- A combination of daclatasvir (60 mg/d)/sofosbuvir (400 mg/d) for 12 weeks*
- A combination of sofosbuvir (400 mg/d)/velpatasvir (100 mg/d) for 12 weeks

Alternative Regimens

- A combination of elbasvir (50 mg/d)/grazoprevir (100 mg/d) for 12 weeks if no baseline NS5A RAS for elbasvir.
- A combination of simeprevir (150 mg/d)/sofosbuvir (400 mg/d) for 12 weeks if there were no basal Q80K mutations*

II.A.2.b. Treatment for G1a Patients with Compensated Cirrhosis

- A combination of ledipasvir (90 mg/d)/sofosbuvir (400 mg/d) plus weight-based ribavirin for 12 weeks or without ribavirin for 24 weeks*.
- A combination of paritaprevir (150 mg/d)/ritonavir (100 mg/d)/ombitasvir (25 mg/d) with dasabuvir (500 mg/d) plus weight-based ribavirin for 24 weeks*.
- A combination of daclatasvir (60 mg/d)/sofosbuvir (400 mg/d) plus weight-based ribavirin for 12 weeks or without ribavirin for 24 weeks *
- A combination of sofosbuvir (400 mg/d) / velpatasvir (100 mg/d) for 12 weeks

Alternative Regimens

- A combination of elbasvir (50 mg/d)/grazoprevir (100 mg/d) for 12 weeks if no baseline NS5A RAS for elbasvir.
- A combination of simeprevir (150 mg/d) /sofosbuvir (400 mg/d) for 24 weeks if there were no basal Q80K mutations*

II.B. Treatment for Patients Infected with Genotype 1b

II.B.1. Treatment-Naive G1b

IIB.1.a. Treatment for Patients without Cirrhosis

- A combination of ledipasvir (90 mg/d)/sofosbuvir (400 mg/d) for 12 weeks*.
  - o Daily fixed dose combination of ledipasvir (90mg/d)/sofosbuvir (400 mg/d) for eight weeks in patients, whose HCV RNA level is <6 million IU/mL
- A combination of paritaprevir (150 mg/d)/ritonavir (100 mg/d)/ombitasvir (25 mg/d) with dasabuvir (500 mg/d) for 12 weeks*
- A combination of daclatasvir (60 mg/d)/sofosbuvir (400 mg/d) for 12 weeks*
- A combination of simeprevir (150 mg/d)/sofosbuvir (400 mg/d) for 12 weeks
- A combination of elbasvir (50 mg/d)/grazoprevir (100 mg/d) for 12 weeks
- A combination of sofosbuvir (400 mg/d) / velpatasvir (100 mg/d) for 12 weeks

Alternative Regimens

- A combination of daclatasvir (60 mg/d)/asunaprevir (400 mg/d) for 24 weeks if no baseline NS5A mutation

II.B.1.b. Treatment for Patients with Compensated Cirrhosis

- A combination of ledipasvir (90 mg/d)/sofosbuvir (400 mg/d) for 12 weeks*.
- A combination of paritaprevir (150 mg/d)/ritonavir (100 mg/d)/ombitasvir (25 mg/d) with dasabuvir (500 mg/d) for 12 weeks*
- A combination of daclatasvir (60 mg/d)/sofosbuvir (400 mg/d) for 12 weeks*
- A combination of simeprevir (150 mg/d) /sofosbuvir (400 mg/d) plus weight-based ribavirin for 12 weeks or without ribavirin for 24 weeks*
- A combination of elbasvir (50 mg/d)/grazoprevir (100 mg/d) for 12 weeks
- A combination of sofosbuvir (400 mg/d)/velpatasvir (100 mg/d) for 12 weeks

Alternative Regimens

- A combination of daclatasvir (60 mg/d) and asunaprevir (400 mg/d) for 24 weeks if no baseline NS5A mutation

II.B.2. Treatment for G1b Patients with Peginterferon/Ribavirin-Experienced

II.B.2.a. Treatment for Patients without Cirrhosis

- A combination of ledipasvir (90 mg/d)/sofosbuvir (400 mg/d) for 12 weeks*.
- A combination of paritaprevir (150 mg/d)/ritonavir (100 mg/d)/ombitasvir (25 mg/d) with dasabuvir (500 mg/d) for 12 weeks*
- A combination of daclatasvir (60 mg/d)/sofosbuvir (400 mg/d) for 12 weeks*

- A combination of simeprevir (150 mg/d)/sofosbuvir (400 mg/d) for 12 weeks*
- A combination of elbasvir (50 mg/d)/grazoprevir (100 mg/d) for 12 weeks
- A combination of sofosbuvir (400 mg/d)/velpatasvir (100 mg/d) for 12 weeks

II.B.2.b. Treatment for Patients with Compensated Cirrhosis

- A combination of ledipasvir (90 mg/d)/sofosbuvir (400 mg/d) plus weight-based ribavirin for 12 weeks or without ribavirin for 24 weeks*.
- A combination of paritaprevir (150 mg/d)/ritonavir (100 mg/d)/ombitasvir (25 mg/d) with dasabuvir (500 mg/d) for 12 weeks*
- A combination of elbasvir (50 mg/d)/grazoprevir (100 mg/d) for 12 weeks
- A combination of daclatasvir (60 mg/d)/sofosbuvir (400 mg/d) plus weight-based ribavirin for 12 weeks or without ribavirin for 24 weeks*
- A combination of simeprevir (150 mg/d)/sofosbuvir (400 mg/d) plus weight-based ribavirin for 12 weeks or without ribavirin for 24 weeks*
- A combination of sofosbuvir (400 mg/d)/velpatasvir (100 mg/d) for 12 weeks

II.C. Treatment for G1 Patients with DAA experience

II.C.1. Treatment for G1 Patients with Sofosbuvir+PegIFN+ Ribavirin-Experienced

II.C.1.a. Treatment for Patients without Cirrhosis

- A combination of ledipasvir (90 mg/d)/sofosbuvir (400 mg/d) plus for 12 weeks*

II.C.1.b. Treatment for Patients with Compensated Cirrhosis

- A combination of ledipasvir (90 mg/d)/sofosbuvir (400 mg/d) plus weight based ribavirin for 24 weeks*

II.C.2. Treatment for G1 Patients with NS3 Protease Inhibitor+ Peginterferon+ Ribavirin-Experienced

II.C.2.a. Treatment for Patients without Cirrhosis

- A combination of ledipasvir (90 mg/d)/sofosbuvir (400 mg/d) for 12 weeks*.
- A combination of daclatasvir (60 mg/d)/sofosbuvir (400 mg/d)) for 12 weeks*
- A combination of sofosbuvir (400 mg/d)/velpatasvir (100 mg/d) for 12 weeks

Alternative Regimens

- A combination of elbasvir (50 mg/d)/grazoprevir (100 mg/d) plus weight-based ribavirin for 16 weeks for patients with baseline NS5A RASs for elbasvir

II.C.2.b. Treatment for Patients with Compensated Cirrhosis

- A combination of ledipasvir (90mg/d)/sofosbuvir (400 mg/d) plus weight-based ribavirin for 12 weeks or without ribavirin for 24 weeks*.
- A combination of daclatasvir (60 mg/d)/sofosbuvir (400 mg/d) plus weight-based ribavirin for 12 weeks or without ribavirin for 24 weeks*
- A combination of sofosbuvir (400 mg/d)/velpatasvir (100 mg/d) for 12 weeks
- A combination of elbasvir (50 mg/d)/grazoprevir (100 mg/d) plus weight-based ribavirin for 16 weeks for patients with baseline NS5A RASs for elbasvir

II.D. Treatment of Patients with Decompensated Cirrhosis

Protease inhibitors treatment should not be used in decompensated patients. From baseline to post-treatment week 12, DAA therapy improves clinical and biochemical parameters including Child-Turcotte-Pugh (CTP) and Model for End-Stage Liver Disease (MELD) scores. Severity of underlying liver disease has an effect on the treatment success. MELD score can be used as a predictor of improvement. MELD score ≥18 may be less likely to improve and may indicate that it's better to underwent liver transplantation (LT) instead of antiviral treatment. Ribavirin should be started with low initial dose (600 mg) and the dose should be titrated according to patients tolerance.

II.D.1a Treatment of Patients with Decompensated Cirrhosis Infected with Genotype 1

- A combination of ledipasvir (90 mg/d)/sofosbuvir (400 mg/d) plus weight-based ribavirin for 12 weeks or without ribavirin for 24 weeks*
- A combination of daclatasvir (60 mg/d)/sofosbuvir (400 mg/d) plus weight-based ribavirin for 12 weeks or without ribavirin for 24 weeks*
- A combination of sofosbuvir (400 mg/d)/velpatasvir (100 mg/d) plus weight-based ribavirin for 12 weeks or without ribavirin for 24 weeks

II.D.1b Treatment of Patients with Decompensated Cirrhosis Infected with Genotype 1 in whom Prior Sofosbuvir- or NS5A-Based Treatment Failed

- A combination of ledipasvir (90 mg/d)/sofosbuvir (400 mg/d) plus weight-based ribavirin for 24 weeks
- A combination of sofosbuvir (400 mg/d)/velpatasvir (100 mg/d) plus weight-based ribavirin for 24 weeks

III. TREATMENT FOR PATIENTS INFECTED WITH GENOTYPE 2

III.A. Treatment for Treatment-Naïve Genotype 2 Patients

III.A.1.a.Treatment for G2 Patients without Cirrhosis

- A combination of daclatasvir (60 mg/d)/sofosbuvir (400 mg/d) for 12 weeks*
- A combination of sofosbuvir (400 mg/d)/velpatasvir (100 mg/d) for 12 weeks

Alternative Regimens

- A combination of sofosbuvir (400 mg/d) with weight-based ribavirin for 12 weeks*

III.A.1.b. Treatment for G2 Patients with Compensated Cirrhosis

- A combination of daclatasvir (60 mg/d)/sofosbuvir (400 mg/d) for 12 weeks*

- A combination of sofosbuvir (400 mg/d)/velpatasvir (100 mg/d) for 12 weeks

Alternative Regimens

- A combination of sofosbuvir (400 mg/d) with weight-based ribavirin for 16-20 weeks*

III.B. Treatment for Peginterferon/Ribavirin-Experienced Genotype 2 Patients

III.B.1.a. Treatment for G2 Patients without Cirrhosis

- A combination of daclatasvir (60 mg/d)/sofosbuvir (400 mg/d) for 12 weeks*
- A combination of sofosbuvir (400 mg/d)/velpatasvir (100 mg/d) for 12 weeks

Alternative Regimens

- A combination of sofosbuvir (400 mg/d) with weight-based ribavirin for 12 weeks*

III.B.1.b. Treatment for Patients with Compensated Cirrhosis

- A combination of daclatasvir (60 mg/d)/sofosbuvir (400 mg/d) for 12 weeks*
- A combination of sofosbuvir (400 mg/d)/velpatasvir (100 mg/d) for 12 weeks

Alternative Regimens

- A combination of daclatasvir (60 mg/d)/sofosbuvir (400 mg/d) for 16-20 weeks*

IV. TREATMENT FOR PATIENTS INFECTED WITH GENOTYPE 3

IV.A. Treatment for Treatment-Naïve Patients

IV.A.1.a Treatment for Patients without Cirrhosis

- A combination of daclatasvir (60 mg/d)/sofosbuvir (400 mg/d) for 12 weeks*
- A combination of sofosbuvir (400 mg/d)/velpatasvir (100 mg/d) for 12 weeks

Alternative Regimens

- A combination of sofosbuvir (400 mg/d) with weight-based ribavirin for 16-20 weeks*

IV.A.1.b. Treatment for Patients with Compensated Cirrhosis

- A combination of daclatasvir (60 mg/d)/sofosbuvir (400 mg/d) plus weight-based ribavirin for 12 weeks or without ribavirin for 24 weeks*
- A combination of sofosbuvir (400 mg/d)/velpatasvir (100 mg/d) plus weight-based ribavirin for 12 weeks

IV.B. Treatment for Peginterferon/Ribavirin-Experienced Genotype 3 Patients

IV.B.1.a Treatment for Patients without Cirrhosis

- A combination of daclatasvir (60 mg/d)/sofosbuvir (400 mg/d) plus weight-based ribavirin for 12 weeks*
- A combination of sofosbuvir (400 mg/d)/velpatasvir (100 mg/d) plus weight-based ribavirin for 12 weeks

IV.B.1.b Treatment for Patients with Compensated Cirrhosis

- A combination of daclatasvir (60 mg/d)/sofosbuvir (400 mg/d) plus weight-based ribavirin for 24 weeks*
- A combination of sofosbuvir (400 mg/d)/velpatasvir (100 mg/d) plus weight-based ribavirin for 12 weeks

V. TREATMENT FOR PATIENTS INFECTED WITH GENOTYPE 4

V.A. Treatment for Treatment-Naive Genotype 4 Patients

V.A.1.Treatment for Patients without Cirrhosis or with Compensated Cirrhosis

- A combination of ledipasvir (90 mg/d) / sofosbuvir (400 mg/d) for 12 weeks*
- A combination of paritaprevir (150 mg/d)/ritonavir (100 mg/d)/ombitasvir (25 mg/d) with weight-based ribavirin for 12 weeks*
- A combination of daclatasvir (60 mg/d)/sofosbuvir (400 mg/d) for 12 weeks*
- A combination of simeprevir (150 mg/d)/sofosbuvir (400 mg/d) for 12 weeks*
- A combination of sofosbuvir (400 mg/d)/velpatasvir (100 mg/d) for 12 weeks
- A combination of elbasvir (50 mg/d)/grazoprevir (100 mg/d) for 12 weeks

V.B. Treatment for Peginterferon/Ribavirin-Experienced Patients

V.B.1. Treatment for Patients without Cirrhosis or with Compensated Cirrhosis

- A combination of ledipasvir (90 mg/d)/sofosbuvir (400 mg/d) plus weight-based ribavirin for 12 weeks or without ribavirin for 24 weeks*
- A combination of paritaprevir (150 mg/d)/ritonavir (100 mg/d)/ombitasvir (25 mg/d) with weight-based ribavirin for 12 weeks*
- A combination of daclatasvir (60 mg/d)/sofosbuvir (400 mg/d) plus weight-based ribavirin for 12 weeks or without ribavirin for 24 weeks*
- A combination of simeprevir (150 mg/d)/sofosbuvir (400 mg/d) plus weight-based ribavirin for 12 weeks*
- A combination of elbasvir (50 mg/d)/grazoprevir (100 mg/d) plus weight-based ribavirin for 12-16 weeks
- A combination of sofosbuvir (400 mg/d)/velpatasvir (100 mg/d) for 12 weeks

VI. TREATMENT FOR PATIENTS INFECTED WITH GENOTYPE 5 OR 6

VI.A. Treatment for Treatment-Naïve Patients

VI.A.1. Treatment for Patients without Cirrhosis or with Compensated Cirrhosis

- A combination of ledipasvir (90 mg/d)/sofosbuvir (400 mg/d) for 12 weeks*
- A combination of daclatasvir (60 mg/d)/sofosbuvir (400 mg/d) for 12 weeks*

- A combination of sofosbuvir (400 mg/d)/velpatasvir (100 mg/d) for 12 weeks

VI.B. Treatment for Treatment-Peginterferon/Ribavirin-Experienced Patients

VI.B.1. Treatment for Patients without Cirrhosis or with Compensated Cirrhosis

- A combination of ledipasvir (90 mg/d)/sofosbuvir (400 mg/d) weight-based ribavirin for 12 weeks*
- A combination of daclatasvir (60 mg/d)/sofosbuvir (400 mg/d) weight-based ribavirin for 12 weeks or without ribavirin for 24 weeks*
- A combination of sofosbuvir (400 mg/d)/velpatasvir (100 mg/d) for 12 weeks

VII. SPECIAL PATIENT POPULATIONS

VII.A. Hepatitis C Treatment after Liver Transplantation

Antiviral treatment for recurrent HCV infection post LT should be started preferably three months after the transplantation. CHC recipients should be treated and followed by gastroenterologist and hepatologist in Transplantation Center.

The drug-drug interaction between DAAs and calcineurin inhibitors is complex and unpredictable. Clinicians should be alert this interaction when antiviral treatment with DAAs is initiated. Calcineurin inhibitors such as tacrolimus levels should be monitored during therapy.

VII.A.1. Treatment for Treatment-naïve and -Experienced Genotype 1,4,5,6 Transplanted Patients

VII.A.1.a Treatment for Patients without Cirrhosis or with Compensated Cirrhosis or Decompensated Cirrhosis

- A combination of ledipasvir (90 mg/d)/sofosbuvir (400 mg/d) plus weight-based ribavirin for 12 weeks or without ribavirin for 24 weeks*
- A combination of daclatasvir (60 mg/d)/sofosbuvir (400 mg/d) plus weight-based ribavirin for 12 weeks or without ribavirin for 24 weeks*
- A combination of sofosbuvir (400 mg/d)/velpatasvir (100 mg/d) plus weight-based ribavirin for 12 weeks or without ribavirin for 24 weeks

VII.A.2. Treatment for Treatment-naïve and -Experienced Genotype 2 or 3 Transplanted Patients

- A combination of daclatasvir (60 mg/d)/sofosbuvir (400 mg/d) plus weight-based ribavirin for 12 weeks in G2 recipients, for 24 weeks in G3 recipients *
- A combination of sofosbuvir (400 mg/d)/velpatasvir (100 mg/d) plus weight-based ribavirin for 12 weeks or 24 weeks in decompensated recipients

VII.B. Patients with HBV Co-Infections

Hepatitis C virus reactivations have been reported in HCV and HBV co-infected patients during or after DAA therapy. Thus, all CHC patients initiating DAA therapy for HCV infection should be assessed for HBV markers. If patients have not experienced for HBV infection, HBV vaccination is recommended. Serum HBV DNA assay should be recommended in patients with HBsAg-positive. Patients meeting treatment criteria for chronic hepatitis B (CHB) infection, antiviral treatment for HBV is recommended at the same time DAA therapy is started. Patients with low or undetectable serum HBV DNA levels can receive HBV prophylaxis or be monitored of serum HBV DNA levels at regular intervals. HBV-experienced patients should be subsequently monitored (serum HBV DNA assay) for HBV reactivation during and after DAAs therapy.

Hepatitis C virus and HBV co-infected patients should be treated as well as patients with chronic HCV monoinfection.

VII.C. Patients with HIV Co-Infections

Liver-related morbidity and mortality and overall mortality are more common in HCV and HIV (Human immunodeficiency virus)-co-infected patients than HCV-monoinfected patients. HIV infection is associated with advance hepatic fibrosis and cirrhosis in co-infected patients. The treatment of CHC patients with HIV co-infections is not different than other CHC patients. The adverse events of antiviral therapy for HCV infection is similar to those observed with HCV monoinfection. The most important point in these co-infected patients is to pay attention to drug-drug interactions that can occur between DAAs and antiretroviral agents. Therefore, for every patient to candidate receiving these treatments, the drug interactions, adverse effects and dose adjustments should be investigated. Physicians should be collaborated with the HIV expert. The presence of HIV co-infection is not a contraindication for LT.

VII.D. Patients with Chronic Kidney Disease

VII.D.1. HCV infection is associated with chronic kidney disease (CKD). Patients with a glomerular filtration rate (GFR) of ≥30 mL/min/1.73m^2 should be treated as same as CHC patients without CKD. No dose adjustment is required.

VII.D.2. Patients with CKD stage 4 or 5 (GFR <30 mL/min/1.73m^2 with/without on dialysis) should be treated if they cannot have renal transplantation. Patients who do not have live donors, but are in the waiting lists for cadaveric transplantations are eligible for CHC treatment because of the long-waiting intervals. These treatments should be administered by experienced centers.

VII.D.2.a. Treatment for Patients with Genotype 1a

- A combination of paritaprevir (150 mg/d)/ritonavir (100 mg/d)/ombitasvir (25 mg/d)/ dasabuvir (600 mg/d) with ribavirin (200 mg/d) for 12 weeks
- A combination of elbasvir (50 mg/d)/grazoprevir (100 mg/d) for 12 weeks

VII.D.2.b. Treatment for Patients with Genotype 1b

- A combination of paritaprevir (150 mg/d)/ritonavir (100 mg/d)/ombitasvir (25 mg/d)/ dasabuvir (600 mg/d) for 12 weeks

- A combination of elbasvir (50 mg/d)/grazoprevir (100 mg/d) for 12 weeks
- A combination of daclatasvir (60 mg/d)/asunaprevir (400 mg/d) for 24 weeks

VII.D.2.c. Treatment for Patients with Genotype 4

- A combination of paritaprevir (150 mg/d)/ritonavir (100 mg/d)/ombitasvir (25 mg/d)/ dasabuvir (600 mg/d) with ribavirin (200 mg/d) for 12 weeks
- A combination of elbasvir (50 mg/d)/grazoprevir (100 mg/d) for 12 weeks

VII.D.2.d. Treatment for Patients with Genotype 2

- A combination of peginterferon and ribavirin (200 mg/d) for 24 weeks

Alternative Regimens

- A combination of daclatasvir (60 mg/d)/sofosbuvir (400 mg/d) for 12 weeks
- A combination of sofosbuvir (400 mg/d)/velpatasvir (100 mg/d) for 12 weeks

VII.D.2.d. Treatment for Patients with Genotype 3

- A combination of peginterferon and ribavirin (200 mg/d) for 24-48 weeks

Alternative Regimens

- A combination of daclatasvir (60 mg/d)/sofosbuvir (400 mg/d) with ribavirin (200 mg/d) for 12 weeks
- A combination of sofosbuvir (400 mg/d)/velpatasvir (100 mg/d) ribavirin (200 mg/d) for 12 weeks

VII.E. Treatment-Naïve and -Experienced Kidney Transplant Recipients

Previous studies have demonstrated the efficacy and safety of DAA therapy in kidney transplant recipients. Various regimens were used. Drug interactions are an important consideration with antiviral therapy in kidney transplant recipients. The use of protease inhibitors is not recommended because of possible drug interactions with immunosuppressive agents.

VII.E.1 Treatment-Naïve and -Experienced Kidney Transplant Recipients with G1 G4, G5, or G6, without Cirrhosis or with Compensated Cirrhosis

- A combination of ledipasvir (90 mg/d)/sofosbuvir (400 mg/d) for 12 weeks
- A combination of daclatasvir (60 mg/d)/sofosbuvir (400 mg/d) for 12 weeks
- A combination of sofosbuvir (400 mg/d)/velpatasvir (100 mg/d) for 12 weeks

VII.E.2 Treatment-Naïve and -Experienced Kidney Transplant Patients with G2, or G3 without Cirrhosis or with Compensated cirrhosis

- A combination of daclatasvir (60 mg/d)/sofosbuvir (400 mg/d) for 12 weeks
- A combination of sofosbuvir (400 mg/d)/velpatasvir (100 mg/d) for 12 weeks

VIII. ACUTE HEPATITIS C TREATMENT

Acute HCV infection spontaneously clears in 20% to 50% of infected individuals. It occurs within six months of the estimated time of acute infection. In past, antiviral treatment with interferons was initiated as early as possible in order to prevent chronicity of acute infection. Currently, there is no consensus regarding when to start DAAs or treatment duration in the treatment of patients with acute HCV infection. Since high efficacy and safety profile of DAAs, it seems to be that no rush is necessary to initiate treatment early. Antiviral therapy is not recommended in spontaneous seroconvertion period. The appropriate time frame to initiate treatment should be at the start of serum ALT elevation. The same treatment approaches for CHC which is described above is recommended.

- A combination of ledipasvir (90 mg/d)/sofosbuvir (400 mg/d) for eight weeks
- A combination of daclatasvir (60 mg/d)/sofosbuvir (400 mg/d) for eight weeks
- A combination of sofosbuvir (400 mg/d)/velpatasvir (100 mg/d) for eight weeks

The treatment duration should be extended, up to 12 weeks in patients with HIV co-infection or in patients with high viral load (HCV RNA level >1 million IU/mL).

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REFERENCES

1. Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med 2014; 370: 1889-98. [CrossRef]
2. Kowdley KV, Gordon SC, Reddy KR, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med 2014; 370: 1879-88. [CrossRef]
3. Reddy KR, Bourlière M, Sulkowski M, et al. Ledipasvir and sofosbuvir in patients with genotype 1 hepatitis C virus infection and compensated cirrhosis: an integrated safety and efficacy analysis. Hepatology 2015; 62: 79-86. [CrossRef]
4. Afdhal N, Reddy KR, Nelson DR, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med 2014; 370: 1483-93. [CrossRef]
5. Curry M, Modi AA, Pungpapong S, et al. Real-world effectiveness of ledipasvir/sofosbuvir (LDV/SOF) in treatment-experienced cirrhotic genotype 1 patients with chronic hepatitis C: a comparative analysis of Gilead sponsored trials with 4 real-world cohorts. J Hepatol 2016; 64: S797. [CrossRef]
6. Bourlière M, Bronowicki JP, de Ledinghen V, et al. Ledipasvir-sofosbuvir with or without ribavirin to treat patients with HCV genotype 1 infection and cirrhosis non-responsive to previous protease inhibitor therapy: a randomized, double-blind, phase 2 trial (SIRIUS). Lancet Infect Dis 2015; 15: 397-404. [CrossRef]
7. Younossi ZM, Stepanova M, Pol S, Bronowicki JP, Carrieri MP, Bourlière M. The impact ofledipasvir/sofosbuvir on patient-reported outcomes in cirrhotic patients with chronic hepatitis C: the SIRIUS study. Liver Int 2016; 36: 42-8. [CrossRef]
8. Osinusi A, Kohli A, Marti MM, et al. Re treatment of chronic hepatitis C virus genotype 1 infection after relapse: an open-label pilot study. Ann Intern Med 2014; 161: 634-8. [CrossRef]

9. Wyles D, Pockros P, Morelli G, et al. Ledipasvir-sofosbuvir plus ribavirin for patients with genotype 1 hepatitis C virus previously treated in clinical trials of sofosbuvir regimens. Hepatology 2015; 61: 1793-7. [CrossRef]
10. Feld JJ, Kowdley KV, Coakley E, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med 2014; 370: 1594-603. [CrossRef]
11. Ferenci P, Bernstein D, Lalezari J, et al. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. N Engl J Med 2014; 370: 1983-92. [CrossRef]
12. Zeuzem S, Jacobson IM, Baykal T, et al. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med 2014; 370: 1604-14. [CrossRef]
13. Andreone P, Colombo MG, Enejosa JV, et al. ABT-450, ritonavir, ombitasvir, and dasabuvir achieves 97% and 100% sustained virologic response with or without ribavirin in treatment-experienced patients with HCV genotype 1b infection. Gastroenterology 2014; 147: 359-65. [CrossRef]
14. Poordad F, Hezode C, Trinh R, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. N Engl J Med 2014; 370: 1973-82. [CrossRef]
15. Feld JJ, Jacobson IM, Hézode C, et al. Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. N Engl J Med 2015; 373: 2599-607. [CrossRef]
16. Pianko S, Flamm SL, Shiffman ML, et al. Sofosbuvir plus velpatasvir combination therapy for treatment-experienced patients with genotype 1 or 3 hepatitis C virus infection: a randomized trial. Ann Intern Med 2015; 163: 809-17. [CrossRef]
17. Gane EJ, Shiffman ML, Etzkorn K, et al. Sofosbuvir/Velpatasvir in combination with ribavirin for 24 weeks ıs effective retreatment for patients who failed prior NS5A containing DAA regimens: results of the retreatment study. 51st Annual Meeting of the European Association for the Study of the Liver (EASL); 2016 April 13-17; Barcelona, Spain.
18. Pol S, BourliereM, Lucier S, et al. Safety and efficacy of daclatasvir-sofosbuvir in HCV genotype 1-mono-infected patients. J Hepatol 2017; 66: 39-47. [CrossRef]
19. Zeuzem S, Ghalib R, Reddy KR, et al. Grazoprevir elbasvir combination therapy for treatment-naive cirrhotic and non cirrhotic patients with chronic hepatitis C virus genotype 1, 4, or 6 infection: a randomized trial. Ann Intern Med 2015; 163: 1-13. [CrossRef]
20. Kwo P, Gane EJ, Peng CY, et al. Effectiveness of elbasvir and grazoprevir combination, with or without ribavirin, for treatment-experienced patients with chronic hepatitis C infection. Gastroenterology 2017; 152: 164-75. [CrossRef]
21. Buti M, Gordon SC, Zuckerman E, et al. Grazoprevir, elbasvir, and ribavirin for chronic hepatitis C virus genotype 1 ınfection after failure of pegylated ınterferon and ribavirin with an earlier-generation protease ınhibitor: final 24-week results from C SALVAGE. Clin Infect Dis 2016; 62: 32-6. [CrossRef]
22. Forns X, Gordon SC, Zuckerman E, et al. Grazoprevir and elbasvir plusribavirin for chronic HCV genotype-1 infection after failure of combination therapy containing a direct-acting antiviral agent. J Hepatol 2015; 63: 564-72. [CrossRef]
23. Lawitz E, Sulkowski MS, Ghalib R, et al. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: the COSMOS randomised study. Lancet 2014; 384: 1756-65. [CrossRef]
24. Lawitz E, Matusow G, DeJesus E, et al. Simeprevir plus sofosbuvir in patients with chronic hepatitis C virus genotype 1 infection and cirrhosis: a phase 3 study (OPTIMIST-2). Hepatology 2016; 64: 360-9. [CrossRef]
25. Sulkowski MS, Vargas HE, Di Bisceglie AM, et al. Effectiveness of simeprevir plus sofosbuvir, with or without ribavirin, in real-world patients with HCV genotype 1 ınfection. Gastroenterology 2016; 150: 419-29. [CrossRef]
26. Hézode C, Chevaliez S, Scoazec G, et al. Retreatment with sofosbuvir and simeprevir of patients with hepatitis C virus genotype 1 or 4 who previously failed a daclatasvir-containing regimen. Hepatology 2016; 63: 1809-16. [CrossRef]
27. Manns M, Pol S, Jacobson IM, et al. All-oral daclatasvir plus asunaprevir for hepatitis C virus genotype 1b: a multinational, phase 3, multicohort study. Lancet 2014; 384: 1597-605. [CrossRef]
28. Kumada H, Suzuki Y, Ikeda K, et al. Daclatasvir plus asunaprevir for chronic HCV genotype 1b infection. Hepatology 2014; 59: 2083-91. [CrossRef]
29. Foster GR, Afdhal N, Roberts SK, et al. Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection. N Engl J Med 2015; 373: 2608-17. [CrossRef]
30. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med 2014; 370: 211-21. [CrossRef]
31. Zeuzem S, Dusheiko GM, Salupere R, et al. Sofosbuvir and ribavirinin HCV genotypes 2 and 3. N Engl J Med 2014; 370: 1993-2001. [CrossRef]
32. Mangia A, Susser S, Piazzolla V, et al. Sofosbuvir and ribavirin for genotype 2 HCV infected patients with cirrhosis: a real-life experience. J Hepatol 2017; 66: 711-7. [CrossRef]
33. Welzel TM, Nelson DR, Morelli G, et al. Effectiveness and safety of sofosbuvir plus ribavirin for the treatment of HCV genotype 2 infection: results of the real-world, clinical practice HCV-TARGET study. Gut 2017; 66: 1844-52 [CrossRef]
34. Omata M, Nishiguchi S, Ueno Y, et al. Sofosbuvir plus ribavirinin Japanese patients with chronic genotype 2 HCV infection: an open-label, phase 3 trial. J Viral Hepat 2014; 21: 762-8. [CrossRef]
35. Nelson DR, Cooper JN, Lalezari JP, et al. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase lll study. Hepatology 2015; 61: 1127-35. [CrossRef]
36. Leroy V, Angus P, Bronowicki JP, et al. Daclatasvir, sofosbuvir, and ribavirin for hepatitis C virus genotype 3 and advanced liver disease: A randomized phase III study (ALLY-3+). Hepatology 2016; 63: 1430-41. [CrossRef]
37. Hézode C, Asselah T, Reddy KR, et al. Ombitasvir plus paritaprevir plus ritonavir with or without ribavirin in treatment-naive and treatment-experienced patients with genotype 4 chronic hepatitis C virus infection (PEARL-I): a randomized, open-label trial. Lancet 2015; 385: 2502-9. [CrossRef]
38. Asselah T, Hézode C, Qaqish RB, et al. Ombitasvir, paritaprevir, and ritonavir plus ribavirin inadults with hepatitis C virus genotype 4 infection and cirrhosis (AGATE I): a multicentre, phase3, randomised open-label trial. Lancet Gastroenterol Hepatol 2016; 1: 25-35. [CrossRef]
39. Waked I, Shiha G, Qaqish RB, et al. Ombitasvir, paritaprevir, and ritonavir plus ribavirin for chronic hepatitis C virus genotype 4 infection in Egyptian patients with or without compensated cirrhosis (AGATE-II): a multicentre, phase 3, partly randomised open-label trial. Lancet Gastroenterol Hepatol 2016; 1: 36-44. [CrossRef]
40. Kohli A, Kapoor R, Sims Z, et al. Ledipasvir and sofosbuvir for hepatitis C genotype 4: a proof-of-concept, single centre, open-label phase 2 a cohort study. Lancet Infect Dis 2015; 15: 1049-54. [CrossRef]
41. Abergel A, Metivier S, Samuel D, et al. Ledipasvir plus sofosbuvir for 12 weeks in patients with hepatitis C genotype 4 infection. Hepatology 2016; 64: 1049-56. [CrossRef]
42. Asselah T, Hendrick W, Reesink, et al. High efficacy of elbasvir and grazoprevir with or without ribavirin in 103 treatment-naïve and experienced patients with HCV genotype 4 infection: a pooled analysis. 66th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD); 2015 November 13-17; San Francisco, USA.
43. Abergel A, Asselah T, Metivier S, et al. Ledipasvir-sofosbuvir in patients with hepatitis C virus genotype 5 infection: an open-label, multicentre, single-arm, phase 2 study. Lancet Infect Dis 2016; 16: 459-64. [CrossRef]