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Review Article

Current treatment of hepatitis C infection

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Abstract

Hepatitis C Virus (HCV) is a RNA virus causing HCV infection. HCV infection is an important cause of cirrhosis, hepatocellular carcinoma (HCC), and death. Interferons were the first agents used to treat HCV infection. Low success rates and serious side effects limited the use of interferons. The discovery of direct-acting antivirals (DAAs), stemming from a deep understanding of the virus's structure, life cycle, and viral proteins, has led to significant advancements in treatment. Currently, all patients infected with HCV can be treated with a high success rate. Thanks to pangenotypic treatments, it is not necessary to determine the genotype of the virus before treatment. DAAs are safer in terms of side effects. Cirrhosis status, comorbidities, and drug-drug interactions should be considered when planning treatment. The World Health Organization (WHO) aims to eliminate hepatitis C infection by 2030. In order to achieve this elimination, patients need to be diagnosed and receive effective treatment. DAAs are effective tools to achieve this aim. In this review, the microbiology, epidemiology, diagnosis, and treatment of HCV infection are presented. Treatment is described in detail from past to present.

Keywords: Antiviral agents, direct-acting antivirals, hepatitis C, treatment.

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INTRODUCTION

Hepatitis C virus (HCV) is an enveloped RNA virus belonging to the *Hepacivirus* genus of the Flaviviridae family (1). HCV was discovered in 1989, and the discovery led the scientists to win the 2020 Nobel Prize in medicine (2). HCV genome encodes a single polyprotein, which is cleaved by viral and host proteases into tenviral proteins (3). These proteins consist of two main categories: structural and non-structural. Structural proteins are Core, E1 and E2. Non-structural proteins are proteases (NS2, NS3, and NS4A), helicase (NS3), and RNA-dependent RNA polymerase (NS5B). NS5A is also a non-structural protein and regulates viral replication and assembly (4,5).

Hepatitis C viruses are divided into six genotypes based on similarities in nucleotide sequences (6). Genotypes are numbered in order of discovery date. Genotypes are also divided into subtypes, which are indicated by lowercase letters. Genotype 1 is the most common and accounts for 46.2% of all HCV cases (7). HCV genotyping has been important for determining treatment.

Hepatitis C infection is an important cause of cirrhosis, hepatocellular carcinoma (HCC), and death (8). Acute hepatitis C infection is mostly asymptomatic and leads to chronic infection in 70-80% of cases, and patients with chronic infection may develop complications such as cirrhosis and cancer (9). World Health Organization (WHO) estimates that in 2023, 58 million people have chronic HCV infection (10). The latest data on mortality is from 2019, and it is estimated that around 290,000 people died from HCV infection in that year (10). Based on a study conducted in 2015, the regions with the highest HCV prevalence in the world are the Eastern Mediterranean (2.3%) and Europe (1.5%) (11). In Turkey, HCV prevalence is approximately 1% (12). In 2016, WHO approved the Global Strategy to eliminate HCV infection by 2030 (13).

The main routes of transmission of HCV infection are parenteral and sexual (14). Risk factors for HCV infection include blood transfusions performed during periods when donors were not screened (before 1992), intravenous drug use, hemodialysis, being born to an HCV-infected mother, tattoos performed under inappropriate settings, and high-risk sexual behaviors (15). Since HCV is usually asymptomatic, screening programs are important to identify people with chronic HCV infection. The American Association for the Study of Liver Diseases– Infectious Diseases Society of America (AASLD-IDSA) guidelines recommend testing for HCV at least once in a lifetime for all adults (16).

The incubation period of hepatitis C is 15-180 days. Approximately 20-30% of patients with acute HCV infection exhibit symptoms. Symptoms include fatigue, nausea and vomiting, abdominal pain, and jaundice. A fulminant course is very rare. HCV-RNA can be detected in serum one week after exposure to the virus. ALT and AST rise rapidly two-eight weeks after infection. Anti-HCV occurs later (four-ten weeks). The severity of the disease is not related to genotype, viral load, gender, or age (17). Chronic HCV infection is usually asymptomatic. Approximately 70-80% of patients experience a stable course, while 20-30% of patients develop cirrhosis. Roughly 5% of patients progress to decompensated cirrhosis each year, while 1-2% of patients develop hepatocellular carcinoma (HCC) annually (18). Extrahepatic manifestations may also be seen in chronic HCV infection. Some of these manifestations are essential mixed cryoglobulinemia, leukocytoclastic vasculitis, membranoproliferative glomerulonephritis, autoimmune thyroiditis, type 2 diabetes mellitus, and sensory or sensorimotor polyneuropathy (19).

Serological tests and nucleic acid amplification tests (NAATs) are used to diagnose HCV infection. Anti-HCV antibodies are used as a screening test. The test methods include enzyme immunoassay (EIA), chemiluminescence microparticle immunoassay (CMIA), and chemiluminescence immunoassay (CIA) (20). In cases with positive anti-HCV antibodies, a quantitative or qualitative HCV-RNA test should be performed to determine whether active infection is present. It should be kept in mind that the window period in acute HCV infections is eight-eleven weeks, and anti-HCV antibodies may not be detected during this period. On the other hand, HCV-RNA becomes positive within one-two weeks after infection (21). After the discovery of pan-genotypic therapies, routine genotype analysis is no longer recommended. Treatment is recommended for almost all HCV-RNA positive cases with few

exceptions. All patients should be treated except those with a life expectancy of less than one year. After the diagnosis of active HCV infection is made, patients should be evaluated for various factors such as cirrhosis status, treatment experience, comorbidities, and concomitant medications (22).

Treatment

Interferons (IFN) were the first agents used in the treatment of HCV infection. IFN was first described in 1957. The use of IFN in the treatment of HCV coincided with the discovery of the virus (23). Given for 24 or 48 weeks, interferons were used alone until ribavirin was added to the treatment in 1998. Pegylated IFNα and ribavirin combination was the standard treatment in the 2000s. While sustained virological response (SVR) was around 15-20% with IFN monotherapy, SVR increased to 40-50% with peg IFNα -ribavirin combination. The numerous side effects of IFN therapy, including flu-like symptoms, bone marrow suppression, muscle pain, and depression, have restricted its widespread use (24).

In 2011, the first direct-acting antivirals (DAAs), boceprevir and telaprevir, were approved by the FDA. They were NS3/4A protease inhibitors (PIs) and were only effective for genotype 1. Boceprevir and telaprevir bind covalently but reversibly to the NS3 serine proteaseto inhibit viral replication in HCV-infected host cells. These DAAs, which should be used in combination with interferon-ribavirin therapy, increased SVR to 70% but were not widely used due to their demanding dosing regimens and various side effects (22).

After 2013, a new era in hepatitis C treatment has begun. The new DAAs that were licensed could be used without IFN, and SVR rates exceeded 90%. After the discovery of pangenotypic therapies, the goal of HCV elimination and eradication has made great progress (8,25). The new DAAs target various stages of HCV replication. Drugs targeting NS3/4A protease include the suffix "-previr,","drugs inhibiting NS5B polymerase have the suffix "-buvir" and NS5A inhibitors end with "-asvir" (26).

The sofosbuvir/ledipasvir combination was approved as a single tablet regimen in 2014. Ledipasvir, which is a NS5A inhibitor, is used at a dose of 90 mg and sofosbuvir 400 mg. Sofosbuvir is a pangenotypic NS5B inhibitor. This combination is used to treat genotypes 1, 4, 5, and 6. Treatment is 12 weeks for the indicated genotypes in treatment-naive, non-cirrhotic patients or patients with compensated cirrhosis. For patients with decompensated cirrhosis, the duration of treatment is 12 weeks with ribavirin or 24 weeks without ribavirin. Sofosbuvir/ledipasvir has been associated with high 12 weeks SVR rates (≥93%) in both treatment-naive and experienced patients, regardless of treatment duration (8, 12, or 24 weeks) or whether administered with or without ribavirin in genotype 1 infections. In genotypes 4, 5, and 6, SVR is also >90%. The most common side effects reported with this treatment are fatigue, headache, asthenia, and nausea (27).

Paritaprevir/ritonavir/ombitasvir with dasabuvir (PrOD) is a combination of the NS5A inhibitor ombitasvir (OBV), the NS3/4A PI paritaprevir (PTV) boosted with ritonavir (r) and the NS5B polymerase inhibitor dasabuvir (DSV). This treatment may be used with or without ribavirin. Treatment regimens according to genotypes are as follows: Genotype 1b, with or without compensated cirrhosis (Child-Pugh A): PrOD for 12 weeks; Genotype 1a, without cirrhosis: PrOD plus ribavirin plus ribavirin for 12 weeks; Genotype 1a, with compensated cirrhosis (Child-Pugh A): PrOD plus ribavirin plus ribavirin for 24 weeks; Genotype 4, without cirrhosis or with compensated cirrhosis (Child-Pugh A): Ombitasvir/paritaprevir/ritonavir plus ribavirin for 12 weeks (no dasabuvir). Twelve weeks SVR rate is high (>95%). An advantage of this regimen is that it is suitable for patients with end-stage kidney disease (28).

The Elbasvir/grazoprevir combination is in single tablet form and contains 50 mg elbasvir and 100 mg grazoprevir. Elbasvir is an inhibitor of NS5A. Grazoprevir is an inhibitor of the NS3/4A protease. These drugs are used for 12 weeks in genotype 1 and 4 infection. In various publications, SVR >95% has been found. The most common adverse effects are fatigue and headache (29).

Sofosbuvir/velpatasvir/voxilaprevir combination is also available in single tablet form and contains

400 mg sofosbuvir, 100 mg velpatasvir and 100 mg voxilaprevir. Sofosbuvir is a nucleotide analog NS5B polymerase inhibitor, velpatasvir is an NS5A replication complex inhibitor, and voxilaprevir is an NS3/4APl. This combination is pangenotypic. For patients without cirrhosis, eight weeks of treatment is recommended, and for patients with compensated cirrhosis, 12 weeks of treatment is recommended. Real-life data of this triple combination therapy showed an SVR of up to 100% (30). The Sofosbuvir/velpatasvir dual combination is also available as a single tablet. It is used for 12 weeks for all genotypes (31).

The combination of Glecaprevir/pibrentasvir consists of 300 mg Glecaprevir and 120 mg Pibrentasvir. It is taken as three tablets (100 mg Glecaprevir and 40 mg pibrentasvir in each tablet) once daily after a meal. Both molecules have a pangenotypic effect. Treatment is given for eight weeks in non-cirrhotic and compensated cirrhotic patients of all genotypes. SVR is >95%. This treatment is usually well-tolerated by patients. The most common side effects are headache and fatigue (32).

In patients with decompensated cirrhosis, treatment options are sofosbuvir/ledipasvir and sofosbuvir/velpatasvir with or without ribavirin (33). In non-cirrhotic patients previously treated with drugs other than NS5A inhibitors, the duration of treatment is 12 weeks with sofosbuvir/velpatasvir/voxilaprevir or eight weeks with glecaprevir/pibrentasvir. In compensated cirrhotic patients with previous treatment experience using drugs other than NS5A inhibitors, the treatment duration is 12 weeks with sofosbuvir/velpatasvir/voxilaprevir or 12 weeks with glecaprevir/pibrentasvir. In non-cirrhotic or compensated cirrhotic patients with previous experience of treatment with NS5A inhibitors or PIs, the duration of treatment is 12 weeks with sofosbuvir/velpatasvir/voxilaprevir or a total of 16 weeks with glecaprevir/pibrentasvir with or without ribavirin. For patients with decompensated cirrhosis and HCV Genotype la, lb, 4, 5, 6 with previous experience of treatment with NS5A inhibitor or PI drugs, the duration of treatment with sofosbuvir/ledipasvir and ribavirin is 24 weeks (16).

Adolescents aged 12-17 years without cirrhosis or with compensated cirrhosis can be treated similarly to adults, regardless of treatment experience. Combinations of sofosbuvir/velpatasvir or glecaprevir/pibrentasvir can be used in treatment. In children aged 3-11 years, these treatments can be given with dose adjustment according to weight (33).

Most DAAs are classified as pregnancy category B. However, there is not yet an approved HCV treatment for pregnant women due to a lack of adequate data. Treatment may be considered on a case-by-case basis (34). There are also some drug studies that have shown that DAAs are safe in pregnant women (35). Breastfeeding of HCV-infected mothers is not contraindicated.

Patients with moderate (30<eGFR<60 ml/min/1.73 m^2) or severe (eGFR <30 ml/min/1.73 m^2) renal insufficiency or patients on hemodialysis can be treated for HCV with the same regimens in the general population (glecaprevir/pibrentasvir or sofosbuvir/velpatasvir) with no dosage adjustment (36).

Recently acquired HCV infection (also called acute HCV infection) is defined as the presence of anti-HCV antibodies and/or HCV-RNA that were not present in previous tests up to 12 months. Acute HCV infection is usually asymptomatic but has a high rate of chronicity. EASL and AASLD-IDSA guidelines recommend treatment of recently acquired HCV infection with glecaprevir/pibrentasvir or sofosbuvir/velpatasvir for eight weeks (16,33).

Patients should have a quantitative HCV RNA level before starting treatment and 12 weeks after completion of treatment. An undetectable HCV RNA 12 weeks or 24 weeks after treatment is considered a sustained virologic response (SVR12 and SVR24) and an effective cure for almost all patients. If patients are not at risk of HCV reinfection, HCV RNA monitoring is not necessary after achieving SVR. For patients with risk factors, HCV RNA measurements should continue to be performed every six months for HCV reinfection. Patients with advanced fibrosis should be screened for HCC with ultrasound and α-fetoprotein levels every sixmonths (37). Hepatitis B reactivation can occur during HCV treatment in patients with HBV/HCV coinfection (38).

CONCLUSION

Significant progress has been made on the hepatitis C virus, which was discovered about 35 years ago. Hepatitis C infection has become a treatable disease with a very high success rate. Current treatments are safe and provide >95% success rate with treatment durations of 8-12 weeks. All patients with hepatitis C viremia should be evaluated thoroughly, and appropriate DAA should be initiated.

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References

1. Li HC, Lo SY. Hepatitis C virus: Virology, diagnosis and treatment. World J Hepatol. 2015;7:1377-89.
2. Laugi H. Discovery of Hepatitis C Virus: 2020 Nobel Prize in Medicine. Euroasian J Hepatogastroenterol. 2020;10:105-8.
3. Marcotrigiano J, Catanese MT. The Structure of HCV. Hepatitis C Virus I: Cellular and Molecular Virology. 2016:31-64
4. Ergünay K, Abacioglu H. Hepatit C Virusunun Genomik Varyasyonları ve Kliniğe Etkileri. (Turkish) Mikrobiyoloji Bülteni. 2015;49:625-35.
5. Weiser BM, Tellinghuisen TL. Structural biology of the hepatitis C virus proteins. Drug Discov Today Technol. 2012;9:e175-226.
6. Barut HŞ, Günal Ö, Dünyada ve ülkemizde hepatit C epidemiyolojisi. (Turkish) Klimik Dergisi. 2009;22:38-43
7. Messina JP, Humphreys I, Flaxman A, Brown A, Cooke GS, Pybus OG, et al. Global distribution and prevalence of hepatitis C virus genotypes. Hepatology. 2015;61:77-87.
8. Di Marco L, La Mantia C, Di Marco V. Hepatitis C: Standard of Treatment and What to Do for Global Elimination. Viruses. 2022;14:505.
9. Roudot-Thoraval F. Epidemiology of hepatitis C virus infection. Clin Res Hepatol Gastroenterol. 2021;45:101596.
10. World Health Organization. Hepatitis C. July 2022. Available from: https://www.who.int/news-room/fact-sheets/detail/hepatitis-c
11. Polaris Observatory HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterol Hepatol. 2017;2:161-76.
12. Tozun N, Ozdogan O, Cakaloglu Y, Idilman R, Karasu Z, Akarca U, et al. Seroprevalence of hepatitis B and C virus infections and risk factors in Turkey: a fieldwork TURHEP study. Clin Microbiol Infect. 2015;21:1020-6.
13. WHO. Combating Hepatitis B and C to Reach Elimination by 2030; World Health Organization: Geneva, Switzerland, 2016.
14. Soza A, Riquelme A, Arrese M. Routes of transmission of hepatitis C virus. Ann Hepatol. 2010;9 Suppl:33.
15. Shaffer M, Ahuja D. Hepatitis C: Screening changes, treatment advances. J Fam Pract. 2017;66:136-44.
16. Bhattacharya D, Aronsohn A, Price J, Lo Re V; AASLD-IDSA HCV Guidance Panel. Hepatitis C Guidance 2023 Update: AASLD-IDSA Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. Clin Infect Dis. 2023; ciad319.
17. Loomba R, Rivera MM, McBurney R, Park Y, Haynes-Williams V, Rehermann B, et al. The natural history of acute hepatitis C: clinical presentation, laboratory findings and treatment outcomes. Aliment Pharmacol Ther. 2011;33:559-65.
18. Manns MP, Buti M, Gane E, Pawlotsky JM, Razavi H, Terrault N, et al. Hepatitis C virus infection. Nat Rev Dis Primers. 2017;3:17006.
19. Kuna L, Jakab J, Smolic R, Wu GY, Smolic M. HCV Extrahepatic Manifestations. J Clin Transl Hepatol. 2019;7:172-82.
20. Gupta E, Bajpai M, Choudhary A. Hepatitis C virus: Screening, diagnosis, and interpretation of laboratory assays. Asian J Transfus Sci. 2014;8:19-25
21. Glynn SA, Wright DJ, Kleinman SH, Hirschkorn D, Tu Y, Heldebrant C, et al. Dynamics of viremia in early hepatitis C virus infection. Transfusion. 2005;45:994-1002.
22. Kish T, Aziz A, Sorio M. Hepatitis C in a New Era: A Review of Current Therapies. P T. 2017;42:316-29.
23. Davis GL, Balart LA, Schiff ER, Lindsay K, Bodenheimer HC Jr, Perrillo RP, et al. Treatment of chronic hepatitis C with recombinant interferon alfa. A multicenter randomized, controlled trial. N Engl J Med. 1989;321:1501-6.
24. Heim MH. 25 years of interferon-based treatment of

chronic hepatitis C: an epoch coming to an end. Nat Rev Immunol. 2013;13:535-42.

25. Dore GJ, Martinello M, Alavi M, Grebely J. Global elimination of hepatitis C virus by 2030: why not? Nat Med. 2020;26:157-60.

26. Cheinquer H. Treatment of chronic hepatitis C virus infection in the near future. Ann Hepatol. 2013;12:854-59.

27. Scott LJ. Ledipasvir/Sofosbuvir: A Review in Chronic Hepatitis C. Drugs. 2018;78:245-56.

28. El-Sayed M, Elserafy M, El Raziky M, Elakel W, Saad Y, Fayad T, et al. Efficacy and safety ofombitasvir/paritaprevir/ritonavir-based therapy in HCV patients with chronic kidney disease. Arab J Gastroenterol. 2023;24:29-33.

29. Hernández-Conde M, Fernández I, Perelló C, Gallego A, Bonacci M, Pascasio JM, et al. Effectiveness and safety of elbasvir/grazoprevir therapy in patients with chronic HCV infection: Results from the Spanish HEPA-C real-world cohort. J Viral Hepat. 2019;26:55-64.

30. Damar Çakırca T, Yamazhan T, Yüksekkaya E, Akgül F, Kurtaran B, Karaşahin Ö, et al. Sofosbuvir/Velpatasvir/Voxilaprevir Experience in Treatment-Naive Chronic Hepatitis C Patients: Preliminary Findings of Real World Data. Viral Hepat J. 2023;29:58-63.

31. Mir F, Kahveci AS, Ibdah JA, Tahan V. Sofosbuvir/velpatasvir regimen promises an effective pan-genotypic hepatitis C virus cure. Drug Des Devel Ther. 2017;11:497-502.

32. Yaras S, Demir M, Barutcu S, Yildirim AE, Gurel S, Ucbilek E, et al. The efficacy and tolerability of glecaprevir/pibrentasvir treatment in a real-world chronic hepatitis C patients cohort. Hepatol Forum. 2023;4:92-6.

33. European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C: Final update of the series [published correction appears in J Hepatol. 2023;78:452]. J Hepatol. 2020;73:1170-218.

34. Kushner T, Terrault NA. Hepatitis C in Pregnancy: A Unique Opportunity to Improve the Hepatitis C Cascade of Care. Hepatol Commun. 2018;3:20-8.

35. Chappell CA, Scarsi KK, Kirby BJ, Suri V, Gaggar A, Bogen DL, et al. Ledipasvir plus sofosbuvir in pregnant women with hepatitis C virus infection: a phase 1 pharmacokinetic study. Lancet Microbe.2020;1:e200-e208.

36. Fabrizi F, Tripodi F, Cerutti R, Nardelli L, Alfieri CM, Donato MF, et al. Recent Information on Pan-Genotypic Direct-Acting Antiviral Agents for HCV in Chronic Kidney Disease. Viruses. 2022;14:2570.

37. Terrault NA. Care of Patients Following Cure of Hepatitis C Virus Infection. Gastroenterol Hepatol (N Y). 2018;14:629-34.

38. Wang C, Ji D, Chen J, Shao Q, Li B, Liu J, et al. Hepatitis due to Reactivation of Hepatitis B Virus in Endemic Areas Among Patients With Hepatitis C Treated With Direct-acting Antiviral Agents. Clin Gastroenterol Hepatol. 2017;15:132-6.