

Hepatitis C virus: A global view

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Abstract

Hepatitis C virus (HCV) is a global challenge; 130-175 million are chronically infected. Over 350000 die each year from HCV. Chronic HCV is the primary cause of cirrhosis, hepatocellular carcinoma (HCC), and end-stage liver disease. Management of chronic HCV is aimed at preventing cirrhosis, reducing the risk of HCC, and treating extra hepatic complications. New treatments for chronic HCV has been devoted based on direct-acting antivirals, as pegylated interferon (peginterferon) is responsible for many side effects and limits treatment access. Sofosbuvir is the first compound to enter the market with Peginterferon-free combination regimens.

Key words: Hepatitis C; Peginterferon; Sofosbuvir; Direct-acting antivirals

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Core tip: Peginterferon is responsible for many side effects. Direct-acting antiviral drugs represent a breakthrough in hepatitis C virus (HCV) therapy. Sofosbuvir is the first compound to enter the market with Peginterferon-free combination regimens. The next few years are expected to introduce more new drugs in the market of HCV therapy with complete elimination of pegylated interferon and ribavirin combination therapy.

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INTRODUCTION

Hepatitis C is a global health problem as the World Health Organization (WHO), reported 3-4 million people

are newly infected with hepatitis C virus (HCV) per year and 130-170 million people are chronically infected. Over 350000 people die each year from hepatitis C-related liver diseases^[1]. The data on the global prevalence are mostly based on HCV seroprevalence studies^[2]. HCV-infected people are at high risk for developing chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC). HCV accounts for about 27% of cirrhotic cases and about 25% of HCC cases worldwide. However, WHO data are based on published studies and data submitted from different countries and regions. Although HCV is a world epidemic, there is great variability in its distribution in different regions of the world^[1,2] (Table 1).

The highest prevalence rates are reported from developing poor countries in Africa and Asia, while the developed, industrialized nations in Europe and North America have low prevalence rates. Egypt, Pakistan, and China have the highest rates of chronic infection. Unfortunately, there are no good data from African countries, with the exception of Egypt, Morocco, and South Africa. The major transmission route in these countries is thought to be unsafe injections using contaminated equipment as in the case of Egypt, where the HCV epidemic has been mainly attributed to the prolonged use of parenteral anti-schistosomal treatment (antimony potassium tartrate, tartar emetics) with use of non-disposable glass syringes for more than 30 years. Chronic HCV is the most common cause of cirrhosis and the most common indication for liver transplantation in Egypt^[3].

PREVALENCE OF HCV GENOTYPES AND SUBTYPES

HCV classified into seven genotypes (1-7) with multiple subtypes on the basis of phylogenetic and sequence analyses of whole viral genomes^[4,5]. HCV strains belonging to different genotypes differ at 30%-35% of nucleotide sites. Strains that belong to the same subtype differ at < 15% of nucleotide sites^[6]. The distribution of HCV genotypes depend on modes of transmission and ethnic variability^[5].

Genotype 1 is the most common HCV genotype and is estimated to account for 83.4 million (46.2%), with wide geographical distribution, in Northern and Western Europe, Asia, North and South America, and Australia^[4,5]. HCV genotype 2 mostly present in West and Central Africa, as its endemic place of origin^[7,8]. HCV genotype 3 is the next most common genotype after genotype 1 and account for 54.3 million (30.1%) cases globally, about 75% of this number occur in south Asia^[4]. Genotype 4 is characteristic for the Middle East especially Egypt^[7]. The predominant HCV genotype among Egyptians was found to be genotype 4, particularly subtype 4a suggesting an epidemic spread of HCV. However, recent studies revealed that other genotypes and subtypes as 1a, 1b, and 2a are also present indicating that HCV genotypes are extremely variable^[8,9]. Genotype 5 is present only in South Africa^[5,7]. Genotype 6 is endemic in South East

Asia especially in Hong Kong and Southern China^[5,8]. Genotypes 2, 4, and 6 are responsible for the majority of the remaining cases of HCV worldwide after cases caused by genotype 1 and 3, with an estimated 16.5 million (9.1%), 15.0 million (8.3%), and 9.8 million (5.4%) cases, respectively. To date, only one genotype 7 infection has been reported; it was isolated in Canada from a Central African immigrant^[10].

MORBIDITY

Twenty-five percent to thirty percent of chronic infected HCV will suffer from cirrhosis after 20-30 years^[3]. Twenty-five percent or more of cirrhotic patients will develop end-stage liver disease or hepatocellular carcinoma. However, pre-cirrhotic infection is not benign, and many HCV-infected patients suffer from extra-hepatic manifestations such as fatigue, joint affection, depression, insulin resistance, diabetes mellitus, nephropathy and lymphoproliferative disorders which increase the hospitalization for HCV patients by 15% per year^[11-13].

MORTALITY

Chronic HCV infection causing about 2.4 million deaths each year. Recently reported that, the average annual age-adjusted mortality rate of deaths in which HCV was increased by 0.18 deaths per 100000 persons per year^[14].

DIAGNOSIS

HCV is often remains undiagnosed for many years and usually diagnosed accidentally. HCV should be suspected in high risk persons and all patients presenting with increased liver enzymes, or cryptogenic chronic liver disease^[15]. Infection with HCV is diagnosed by testing for specific antibodies using enzyme immunoassay (EIA), chemiluminescence immunoassays and recombinant immunoblot assays^[16]. The introduction of the third generation EIA has brought the specificity of the serological testing to extremely high (greater than 99%)^[17]. The presence of HCV antibodies indicate that HCV infection is acute, chronic, or has resolved. HCV-RNA can be detected in the blood using polymerase chain reaction or transcription-mediated amplification^[18]. HCV-RNA should be determined before initiating treatment and monitoring of HCV treatment^[19]. HCV genotyping is useful in determining treatment duration and predicting the likelihood of treatment response^[20-22].

TREATMENT

Treatment indications

The goal of antiviral therapy is to cure HCV with sustained virological response (SVR). Treatment should be recommended in all chronic HCV infection adult patients especially patients who are at risk of developing cirrhosis unless there are therapy contraindications. Treatment of

Table 1 Hepatitis C prevalence rates in developed and developing countries^[1]

Country	Prevalence
Egypt	18%-22%
Italy	2.5%-10%
Pakistan	4.9%
China	3.2%
Indonesia	2.1%

Table 2 Pretreatment assessments in patients with chronic hepatitis C virus infection^[23]

Medical history, including previous antiviral therapies and response
Psychiatric history, including substance use disorders
Liver function tests, including liver enzymes, serum albumin, serum bilirubin, and prothrombin time
Complete blood count
Thyroid-stimulating hormone
Serum creatinine
Plasma glucose
Pregnancy test (in female of childbearing period)
HIV serology
Hepatitis B surface antigen
Quantitative HCV RNA measurement
Retinal examination
Electrocardiogram

HCV: Hepatitis C virus; HIV: Human immunodeficiency virus.

chronic HCV with pegylated interferon (PegIFN)-alpha and ribavirin (RBV) containing regimens is absolutely contraindicated in: Uncontrolled depression, psychosis or epilepsy; pregnancy; severe concurrent medical diseases including retinopathy, autoimmune thyroid disorders; liver cell failure^[16,23,24].

Now, Pretreatment liver biopsy is not mandatory and instead we can use fibroscan^[25]. Other lines of pretreatment assessment are included in (Table 2).

Until 2011, the combination of PegIFN-alpha and ribavirin for 24 or 48 wk was the standard of care for treatment of HCV infection. PegIFNs administered subcutaneously once weekly in combination with oral RBV, resulting overall SVR rates of 40%-50% among treatment-naïve patients^[21,26]. SVR rates were lower in specific patient populations, such as African Americans^[27]. Adverse events from either PegIFN alpha-2a or alpha-2b, and RBV are similar. The optimal RBV dose appears to be between 800 and 1400 mg per day, based on weight in combination with either PegIFN product^[28]. The standard treatment duration of PegIFN and RBV has been 48 wk, except in patients who are slow responders (detectable HCV RNA at 12 wk but undetectable HCV RNA by 24 wk into treatment), in whom extending therapy to 72 wk may be beneficial^[29,30].

New drugs for hepatitis C

After 2011, new oral effective drugs have been introduced in the treatment of chronic HCV infection with the cure rate about 90%^[31]; suggest that we might soon be able to cure all patients with HCV (treatment-naïve,

relapsed patients on previous treatment and resistant patients). These new drugs open a new era in the management of chronic HCV infection after 25 years of HCV discovery. During these 25 years, the classical line of treatment of HCV had many side effects with limited success and low SVR; the new class of drug is called directly acting antiviral agents (DAAs)^[32].

DAAs drugs increase the SVR rates with fewer side effects and provide a new hope for chronic HCV either naïve or treated patients with simplified route of administration *via* oral intake and more short period for treatment. First-generation NS3 protease inhibitors introduced in the market of HCV therapy since 2011 are telaprevir and boceprevir, which approved as a new standard line of therapy for genotype 1 HCV patients in addition to standard classical therapy, although low SVR rates were obtained in replasers and previous non-responder to dual therapy^[33]. Moreover, many side effects, especially in patients with advanced grade of hepatic fibrosis^[34].

Sofosbuvir (SOF), simeprevir (SIM), and daclatasvir (DCV), are new generations of DAAs which increase the SVR rates with fewer side effects and short duration of treatment. These drugs are used with or without PegIFN and/or RBV combination with different duration of treatment according to combination were used. In IFN eligible patients, the optimal regimen is a 12-wk course of PegIFN and RBV plus SOF, SIM, and DCV, but in IFN ineligible patients, the best line of treatment is 24-wk of SOF/RBV, or 12-wk of SOF-SIM or SOF-DCV with or without RBV. Monotherapy with SOF, SIM, and DCV is not recommended^[35].

SOF as line of treatment of chronic HCV

SOF is pan-genotypic antiviral HCV-specific nucleotide inhibitor of viral NS5B polymerase that acts as chain terminator when incorporated as a substrate by RNA polymerase in the nascent HCV-RNA genome, leading to inhibition of viral replication which has a high barrier to resistance^[36]. SOF is taken at dose of 400 mg once daily oral, without relation to food intake. SOF is taken as prodrug which became active molecule by phosphorylation inside the hepatocytes. SOF is metabolized by dephosphorylation to convert the active molecule to inactive metabolite GS-331007. GS-331007 is excreted through the kidney but the dose modification of SOF is not required if creatinine clearance is ≤ 30 mL/min. In severe renal impairment and end stage renal disease SOF is not recommended. Dose adjustment is not recommended in patients with mild-to-severe hepatic impairment^[37,38].

SOF treatment regimens without PegIFN should not be used for patients with genotype 1, 4, 5 or 6 HCV infection unless the HCV patients had contraindication for PegIFN. Patients with advanced liver fibrosis or cirrhosis, high baseline viral load, previous unresponsiveness to PegIFN and RBV combination therapy may need extended course for 24 wk^[39].

GLOBAL PREVENTION AND CONTROL

In many countries, including the developed countries, most patients with HCV infection are unaware about their infection for many years and, so developed cirrhosis and HCC before they known about their HCV infection and also became a big source of HCV infection in their communities^[40]. In developing countries, barriers to screening include inadequate awareness of hepatitis C among healthcare providers and their patients. Public health officials in many developing countries do not understand the true burden of HCV infection. Surveillance for HCV infection is very important^[41,42]. Linking prevention to testing, and treatment of HCV infection requires a comprehensive approach tailored to meet the needs of individual countries^[43].

CONCLUSION

DAAs drugs represent a breakthrough in HCV therapy. The next few years are expected to introduce more new drugs in the market of HCV therapy with complete elimination of PegIFN and RBV combination therapy.

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