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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MINIREVIEWS

Hepatitis C virus: A global view

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Author contributions: All authors contributed equally to this work.

Conflict-of-interest statement: There is no conflict of interest.

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Received: September 9, 2014
Peer-review started: September 9, 2014
First decision: September 28, 2014
Revised: July 29, 2015
Accepted: November 3, 2015
Article in press: November 4, 2015
Published online: November 18, 2015

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[12-2] (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[7].

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[6,9]. 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 1and 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
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. Until 2011, the combination of PegIFN-alpha and ribavirin for 24 or 48 wk was the standard of care for treatment of HCV infection. PegIFNαs administered subcutaneously once weekly in combination with oral RBV, resulting overall SVR rates of 40%-50% among treatment-naive patients. SVR rates were lower in specific patient populations, such as African Americans. 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. 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.

**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-naive, 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).

**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. SOF is not recommended. Dose adjustment is not required if creatinine clearance is \( \leq \) 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.

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.
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.

REFERENCES

1 World Health Organization. Secretariat. Viral hepatitis. Sixth-Third World Health Assembly A63/15. Provisional agenda item 11.12. Geneva: World Health Organization, 2010
2 Shephard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. Lancet Infect Dis 2005; 5: 558-567 [PMID: 16122679 DOI: 10.1016/S1473-3099(05)70216-4]
3 Seeff LB. Natural history of chronic hepatitis C. Hepatology 2002; 36: S35-S46 [PMID: 12407575 DOI: 10.1053/jhep.2002.38066]
4 Messina JP, Humphreys I, Flaxman A, Brown A, Cooke GS, Pybus OG, Barnes E. Global distribution and prevalence of hepatitis C virus genotypes. Hepatology 2015; 61: 77-87 [PMID: 25069599 DOI: 10.1002/hep.27259]
5 Hajarizadeh B, Grebely J, Dore GJ. Epidemiology and natural history of HCV infection. Nat Rev Gastroenterol Hepatol 2013; 10: 533-562 [PMID: 23817321 DOI: 10.1038/nrgastro.2013.107]
6 Smith DB, Bukh J, Kuiken C, Muerhoff AS, Rice CM, Stapleton JT, Simmonds P. Expanded classification of hepatitis C virus into 7 genotypes and 67 subtypes: updated criteria and genotype assignment web resource. Hepatology 2014; 59: 318-327 [PMID: 24115039 DOI: 10.1002/hep.26744]
7 Karoney MJ, Siika AM. Hepatitis C virus (HCV) infection in Africa: a review. Pan Afr Med J 2013; 14: 44 [PMID: 23560127 DOI: 10.11604/pamj.2013.14.44.2199]
8 Lavanchy D. Evolving epidemiology of hepatitis C virus. Clin Microbiol Infect 2011; 17: 107-115 [PMID: 21091831 DOI: 10.1111/j.1469-0691.2010.03432.x]
9 Daw MA, Dau AA. Hepatitis C virus in Arab world: a state of concern. ScientificWorldJournal 2012; 2012: 719494 [PMID: 22629189 DOI: 10.1100/2012/719494]
10 Murphy DG, Willems B, Deschênes M, Hilzenrat N, Mousseau R, Sabbath S. Use of sequence analysis for routine genotyping of HCV with reference to C/E1 and S’ untranslated region sequences. J Clin Microbiol 2007; 45: 1102-1112 [PMID: 17287328 DOI: 10.1128/JCM.02366-06]
11 Arrese M, Riquelme A, Soza A. Insulin resistance, hepatic steatosis and hepatitis C: a complex relationship with relevant clinical implications. Ann Hepatol 2010; 9 Suppl: 112-118 [PMID: 20714007]
12 Jacobson IM, Cacoub P, Dal Maso L, Harrison SA, Younossi ZM. Manifestations of chronic hepatitis C virus infection beyond the liver. Clin Gastroenterol Hepatol 2010; 8: 1017-1029 [PMID: 20670037 DOI: 10.1016/j.cgh.2010.08.026]
13 Moorman AC, Gordon SC, Rupp LB, Spradling PR, Teshale EH, Lu M, Neronz DR, Nakasato CC, Boscarino JA, Henkle EM, Oja-Tebbe NJ, Xing J, Ward JW, Holmberg SD. Baseline characteristics and mortality among people in care for chronic viral hepatitis: the chronic hepatitis cohort study. Clin Infect Dis 2013; 56: 40-50 [PMID: 22990852 DOI: 10.1093/cid/cis815]
14 Ly KN, Xing J, Kleven RS, Jiles RB, Ward JW, Holmberg SD. The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. Am Intern Med 2012; 156: 271-278 [PMID: 22251712 DOI: 10.7326/0003-4819-156-4-20122210-00004]
15 Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. Centers for Disease Control and Prevention. MMWR Recomm Rep 1998; 47: 1-39 [PMID: 9790221]
16 Ghany MG, Strader DB, Thomas DL, Seeft LB; American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 2009; 49: 1335-1374 [PMID: 19330875 DOI: 10.1002/hep.22799]
17 Colin C, Lanoir D, Touzet S, Meyaud-Kraemer L, Bailly F, Trepo C; HEPATIPPS Group. Sensitivity and specificity of third-generation hepatitis C virus antibody detection assays: an analysis of the literature. J Viral Hepat 2001; 8: 87-95 [PMID: 11264728 DOI: 10.1046/j.1365-2893.2001.00280.x]
18 McHutchison JG, Gordon SC, Schiff ER, Shiffman ML, Lee WM, Rustgi VK, Goodman ZD, Ling MH, Cort S, Albrecht JK. Interferon alpha-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. Hepatitis Interventional Therapy Group. N Engl J Med 1999; 339: 1485-1492 [PMID: 9819446 DOI: 10.1056/NEJM199811393292101]
19 Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Lancet 1997; 349: 825-832 [PMID: 9121257 DOI: 10.1016/S0140-6736(96)67042-8]
20 Friedrich-Rust M, Zeuzem S, Sarrazin C. Current therapy for hepatitis C. Int J Colorectal Dis 2007; 22: 341-349 [PMID: 16175369 DOI: 10.1007/s00053-008-0039-9]
21 Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reinolder R, Goodman ZD, Koury K, Ling M, Albrecht JK. Peginterferon alpha-2b plus ribavirin compared with interferon alpha-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 2001; 358: 958-965 [PMID: 11583749 DOI: 10.1016/S0140-6736(01)06102-5]
22 Hu KQ, Tong MJ. Long-term outcomes of patients with compensated hepatitis C virus-related cirrhosis and history of parenteral exposure in the United States. Hepatology 1999; 29: 1311-1316 [PMID: 10094980 DOI: 10.1002/hep.10290424]
23 Kim AI, Saah S. Treatment of hepatitis C. Am J Med 2005; 118: 808-815 [PMID: 16084169 DOI: 10.1016/j.amjmed.2005.01.073]
24 Sandeep M, Dhawan VK. Hepatitis C Treatment & Management. In: Katz J, editor. Medscape reference, 2012
25 National Institutes of Health Consensus Development Conference Panel statement: management of hepatitis C. Hepatology 1997; 26: 25-105 [PMID: 9305656 DOI: 10.1002/hep.10260701]
26 Fried MW, Shiffman ML, Reddy KR, Smith C, Marinatos G, Gonçales FL, Häussinger D, Diago M, Carosi G, Dhumeaux D, Craxi A, Lin A, Hoffman J, Yu J. Peginterferon alpha-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002; 347: 975-982 [PMID: 12324553 DOI: 10.1056/NEJMoa020047]
27 Muir AJ, Bornstein JD, Kellenig PG. Atlantic Coast Hepatitis Treatment Group. Peginterferon alpha-2b and ribavirin for the treatment of chronic hepatitis C in blacks and non-Hispanic whites. N Engl J Med 2004; 350: 2265-2271 [PMID: 15163776 DOI: 10.1056/NEJMoa032502]
28 Jacobson IM, Brown RS, Freilich B, Afshald N, Kwo PY, Santoro J, Becker S, Wakil AE, Pound D, Godske F, Strauss R, Bernstein D, Flamm S, Pauly MP, Mukhiapaldhay P, Griffel LH, Brass CA.

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Peginterferon alfa-2b and weight-based or flat-dose ribavirin in chronic hepatitis C patients: a randomized trial. *Hepatology* 2007; 46: 971-981 [PMID: 17894303 DOI: 10.1002/hep.21932]

29 Berg T, von Wagner M, Nasser S, Sarrazin C, Heintges T, Gerlach T, Buggisch P, Goeser T, Rasenack J, Pape GR, Schmidt WE, Kallinowski B, Klinker H, Spengler U, Zeuzem S. Extended treatment duration for hepatitis C virus type 1: comparing 48 versus 72 weeks of peginterferon-alfa-2a plus ribavirin. *Gastroenterology* 2006; 130: 1086-1097 [PMID: 16618403 DOI: 10.1053/j.gastro.2006.02.015]

30 Pearlman BL, Ehleben C, Saifee S. Treatment extension to 72 weeks of peginterferon and ribavirin in hepatitis c genotype 1-infected slow responders. *Hepatology* 2007; 46: 1688-1694 [PMID: 18044671 DOI: 10.1002/hep.21919]

31 Kowdley KV, Lawitz E, Poordad F, Cohen DE, Nelson DR, Zeuzem S, Everson GT, Kwo P, Foster GR, Sulkowski MS, Xie W, Pilot-Matias T, Liassios G, Larsen L, Khatri A, Podsadecki T, Bernstein B. Phase 2b trial of interferon-free therapy for hepatitis C virus genotype 1. *N Engl J Med* 2014; 370: 222-232 [PMID: 24428468 DOI: 10.1056/NEJMoai306227]

32 Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. *Science* 1989; 244: 359-362 [PMID: 2523562]

33 Aghemo A, Degasperi E, Colombo M. Directly acting antivirals for the treatment of chronic hepatitis C: unresolved topics from registration trials. *Dig Liver Dis* 2013; 45: 1-7 [PMID: 22695478 DOI: 10.1016/j.dld.2012.05.002]

34 D'Ambrosio R, Colombo M. Safety of direct antiviral agents in real life. *Dig Liver Dis* 2013; 45 Suppl 5: S363-S366 [PMID: 24091117 DOI: 10.1016/j.dld.2013.07.012]

35 Abdel-Razek W, Waked I. Optimal therapy in genotype 4 chronic hepatitis C: finally cured? *Liver Int* 2015; 35 Suppl 1: 27-34 [PMID: 25529085 DOI: 10.1111/liv.12724]

36 Martel-Lafferriere V, Dieterich DT. GS-7977: A promising nucleotide analog NS5B polymerase inhibitor of HCV. *Future Virol* 2012; 7: 537-546

37 Kirby B, Gordi T, Symonds WT, Kearney BP, Mathias A. Population pharmacokinetics of sofosbuvir and its major metabolite (GS-331007) in healthy and HCV-infected adult subjects. 64th Annual Meeting of the American Association for the Study of Liver Diseases. Washington: DC, 2013 Nov 1-5

38 Degasperi E, Aghemo A. Sofosbuvir for the treatment of chronic hepatitis C: between current evidence and future perspectives. *Hepat Med* 2014; 6: 25-33 [PMID: 24022024 DOI: 10.2147/HMER.S44375]

39 NICE technology appraisal in development. Final appraisal determination - sofosbuvir (ID654) for treating chronic hepatitis C. London: NICE, 2015: 1-104

40 Institute of Medicine (US) Committee on the Prevention and Control of Viral Hepatitis Infection, Colvin HM, Mitchell AE. Hepatitis and liver cancer: A national strategy for prevention and control of hepatitis B and C. Washington (DC): National Academies Press (US), 2010

41 Arab Republic of Egypt, Ministry of Health and Population National Committee for the Control of Viral Hepatitis. Egyptian national control strategy for viral hepatitis 2008-2012. [Accessed 2012 Jan 5]. Available from: URL: http://www.pasteur-international.org/ip/resource/filecenter/document/01sz-000402-0da/nsp-10-april-2008-final.pdf

42 Ministry of Health, Government of Pakistan. Prime Minister’s Program for Hepatitis Prevention and Control phase I (2005-2010) and phase II (2010-2015). Report, 2010

43 World Hepatitis Alliance. Viral hepatitis: Global policy. [Accessed 2012 Jan 3]. Available from: URL: http://www.worldhepatitisalliance.org/Libraries/Campaign_Materials/Viral_Hepatitis_Global_Policy.sflb.ashx

P- Reviewer: Herzer K, Parola M  S- Editor: Gong XM  L- Editor: A  E- Editor: Liu SQ
