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Invited Review

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Hepatitis C Viral Infection in Children: Updated Review

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Hepatitis C virus (HCV) infection is a major medical challenge affecting around 200 million people worldwide. The main site of HCV replication is the hepatocytes of the liver. HCV is a positive enveloped RNA virus from the flaviviridae family. Six major HCV genotypes are implicated in the human infection. In developed countries the children are infected mainly through vertical transmission during deliveries, while in developing countries it is still due to horizontal transmission from adults. Minimal nonspecific and brief symptoms are initially found in approximately 15% of children. Acute and chronic HCV infection is diagnosed through the recognition of HCV RNA. The main objective for treatment of chronic HCV is to convert detected HCV viremia to below the detection limit. Children with chronic HCV infection are usually asymptomatic and rarely develop severe liver damage. Therefore, the benefits from current therapies, pegylated-Interferon plus ribavirin, must be weighed against their adverse effects. This combined treatment offers a 50-90% chance of clearing HCV infection according to several studies and on different HCV genotype. Recent direct acting antiviral (DAA) drugs which are well established for adults have not yet been approved for children and young adults below 18 years. The most important field for the prevention of HCV infection in children would be the prevention of perinatal and parenteral transmission. There are areas of focus for new lines of research in pediatric HCV-related disease that can be addressed in the near future.

Key Words: Hepatitis C virus, Hepatitis C viral infection, Children, Epidemiology, Diagnosis treatment, Direct acting antivirals

INTRODUCTION

In 1989 several distinguished researchers from National Institute of Health (NIH), Center for Disease Control (CDC) and industry discovered hepatitis C virus (HCV). It was previously identified as non-A/non-B hepatitis. Other viruses that cause hepatitis include hepatitis A, B, D, E, and G [1]. HCV infection is a major medical challenge affecting around 200 million people worldwide [2,3]. Prevalence of hepatitis C varies from less than 1.0% in European countries and to further than 3% in some African

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countries especially in Egypt where it exceeds 40% in rural areas. The story differs in Egyptian children where prevalence is around 3% [4]. HCV infection leading to chronicity stays usually symptomless during childhood. Nonspecific mild symptoms of fatigue and fever present in only 15% of children at the time of primary diagnosis. Although HCV infection is mostly in the liver, other extrahepatic sites such as lymphoid cells and mononuclear cells are accountable for about 3.1% of the virus load [5].

HEPATITIS C VIRUS

In order to study HCV infection and introduce new therapies and produce vaccines, we need to extensively understand the HCV viral structure and its life cycle. HCV is a positive enveloped RNA virus from the flaviviridae family and is approximately 9600 nucleotides in length. Inside the hepatocyte it is translated and processed to generate structural and non-structural proteins. Structural proteins include core protein, envelope proteins; and nonstructural (NS) proteins include NS2, NS3, NS4A, NS4B, NS5A, and NS5B [6,7].

The structural core is the viral nucleocapsid protein with several functions including the binding of RNA, the modulation of the immunity, the signaling of the cells, the induction of oncogenicity and the presence of autophagy. The structural E1 and E2 proteins are the envelope to the viral particles. These glycoproteins E1 and E2 are attacked by the neutralizing antibodies that have high degree of sequence variations. These variations not only lead to antibody responses ineffectiveness but also cause HCV persistence and chronicity [7-11].

The NS proteins NS2, NS3, NS4A, NS4B, NS5A, and NS5B are indulged in most of the steps of the HCV life cycle, including attaching the viral, entering and fusing, translating HCV RNA, the processing, replicating the HCV, assembling and releasing the virus [7,12].

HEPATITIS C VIRAL LIFE CYCLE AND REPLICATION

The unfolding of the HCV life cycle paved the way for the development of the highly effective therapies. The lack of a suitable animal model for defining the steps of HCV infection (except for the chimpanzee and man) greatly delayed such studies for several years. The availability of tissue-culture using the recombinant DNA technology facilitated advanced scientific research and discovery of the HCV life cycle. This paved the way to the early trials of new therapies as well as the advances that have been achieved into vaccine development [13].

The main site of HCV replication is the hepatocytes of the liver. Other extrahepatic sites of replication is the peripheral blood mononuclear cells, which potentially account for the high levels of immunological disorders and systemic manifestations that are encountered in chronically infected HCV patients. It is anticipated that a total of one trillion virions are produced every day, as each infected cell generates around fifty viral particles [7,8].

Entry of the virus into various host cells occur through complex interactions between virions and cell receptors CD81, low-density lipoprotein (LDL) receptor, SR-BI, DC-SIGN, claudin-1, and occludin [14]. Once inside the host cell, it is uncoated and the polyprotein is translated using the internal ribosome entry site, thus producing a 3,011 amino acids long protein. The viral and cellular proteases mentioned earlier cleave this polyprotein to yield the three structural (virion-associated) and the seven NS proteins. The NS proteins then engage the viral genome into an RNA replication complex. Such replication comprises the creation of a negative strand RNA molecule which template the production of the positive strand RNA. The presence of this negative strand indicates active viral replication [15]. HCV rapid mutation leads to wide variety of genotypes (6 till now) and the high error prone rate of such mutation leads to production of many variants of the virus called quasispecies [16,17].

Nascent genomes after translation and replication

are packaged into new virus particles. These particles are secreted from the hepatocyte through a very low density lipoprotein pathway [18-20].

HEPATITIS C GENOTYPES

Six major HCV genotypes are implicated in the human infection. A person can be infected with one strain or more at a time. Genotypes 1, 2, and 3 are found worldwide, genotype 1 is the most prevalent strain in the American continent. In Northern Africa including Egypt (90%) genotype 4 is the most prevalent, while genotype 5 is prevalent in South Africa. Genotype 6 is the prevalent strain in Asia. Laboratory genotyping is a useful prognostic tool that influences the response rates to therapy. Patients with genotype 1 are the least likely to respond to the conventional peginterferon and ribavirin therapy, and most probably will benefit from the new combination therapy of the direct antiviral drugs [21].

EPIDEMIOLOGY AND TRANSMISSION OF HEPATITIS C INFECTION IN INFANTS AND CHILDREN

HCV infection in children differs from adults in several aspects. In developed countries the children are infected mainly through vertical transmission during deliveries, while in developing countries it is still due to horizontal transmission from adults [22].

The usage of intravenous drugs by the mothers, the presence of HLA-DRB1*10 in children and the existence of HCV RNA in maternal peripheral blood mononuclear cells increase the risk of transmission to children. While the intake of breast milk, food or water and the usual contact such as the hugging and kissing of an infected person are not considered modes of transmission for hepatitis C infection in children [23].

Horizontal transmission was studied extensively in Egypt being the most infected area in the world. Relationship between HCV infection and schistosomiasis were being considered the most prevalent health problems in Egypt. Mass treatment campaigns to control schistosomiasis using tartar emetic injections were undertaken through the years 1960s till 1980s in Egypt. It is postulated that multiple use of improperly sterilized needles in these campaigns facilitated the transmission of HCV in the region. To emphasis this theory, several studies showed that HCV infections are discovered within families in which several members had received tartar emetic injections for schistosomiasis. After introduction of disposable syringes this mode of horizontal transmission have been dramatically reduced [24].

Vertical transmission in infants and children can affect 4% to 10% of infants born to HCV infected mothers. The risk of vertical transmission escalates when mothers are having high viral load and when there is maternal co-infection with human immunodeficiency virus [25]. When the density of maternal HCV was 1 million particles per milliliter, the rate of vertical transmission reached 36% [26].

Anti-HCV antibodies are present in the neonates' blood as a result of passive placental transfer from their infected mothers. These antibodies can persist for the first 12-15 months of life. Thus, the actual definition of mother-to-child (vertical) transmission of HCV means the persistence of anti-HCV antibodies in a child over 18 months of age, or the presence of HCV RNA in an infant older than 2 months of age in two different sampling occasions [27,28]. Thus the suspected infants should be tested for HCV RNA at the age of 2-6 months, and at 18-24 months, along with serum anti-HCV [27]. Umbilical cord blood as well as samples withdrawn before 1 month of age is not advised as they can show high falsely negative and positive results.

Vertical transmission has a high rate of clearance of infection reaching around 90%, while in horizontal transmission clearance can be less than 20%. Several studies addressed clearance of vertical transmission especially in the Middle East and Europe. In Egypt, HCV infection was determined in 10% of the newborns of HCV infected mothers [29]. At 1 year, 5.47% cleared the virus. At 2 to 3 years, 2.1% cleared the virus. The infection persisted in 2.43%.

The follow-up revealed that HCV infection wheth-

er vertically or horizontally progresses to chronicity and its complications much slower in infected children than in adults [30,31].

In Italy, 119 symptomless children were diagnosed within the first 3 years of life, and 5%, 2.5%, 7%, 32% and 6% cleared the infection for genotypes 1a, 1b, 2, 3 and 4, respectively [32]. In another European study from several countries, 155 children were diagnosed at birth, 17% cleared HCV at 2 years of age, 24% at 3 years and 30% at 5 years, with no clearance beyond 5 years [33].

Interventions to prevent vertical transmission are not yet introduced specially in the absence of HCV vaccines. Neither elective caesarean section nor avoiding breastfeeding had been advised as preventive measures [34]. The hope is in the recent safe direct acting antiviral (DAA) drugs that can offer effective prenatal treatment to infected mothers thus abolishing this narrow window of infection.

SYMPTOMS AND COURSE OF HEPATITIS C INFECTION IN CHILDREN

The incubation period for HCV infection ranges from as low as two weeks to as high as six months. As mentioned earlier, more than three quarters of the children are symptomless. Minimal nonspecific and brief symptoms are initially found in approximately 15% of children. These symptoms can be in the form of hyperpyrexia, lethargy, anorexia, nausea, vomiting, and abdominal colic. They can present with deep-colored urine, light-colored feces, arthralgia and yellowish discoloration of skin and sclera. In contrast to adults; cryoglobulinemia, vasculitis and porphyria cutaneatarda are not recorded in children [35]. Only ten% of the chronically infected infants present with hepatomegaly [36], and elevations of asymptomatic aminotransferase may be accidentally encountered [37].

In several European studies, chronicity was apparent in small percentage of infected children. In an Italian study 6 out of 332 (1.8%) infected children developed portal hypertension in the form of ascites and variceal bleeding. Two of them showed these symptoms and signs at an early age (2 and 5 years), while the other 4 was older at the ages of 11-15 years. In another European study, only 0.5% (one out of 194 infected children showed decompensated liver disease and needed liver transplantation at the age of 19 years. All these children were infected with HCV genotype 1a. [30,37,38].

In the USA, a tertiary center described 7 out of 91 children with a mean age of 11 years old to have severe liver disease [39]. Cirrhosis and hepatocellular carcinoma were reported in 2 adolescents 14 years of age in another study [40].

If rare complication are encountered, therapeutic invasive interventions may be necessary such as in portal hypertension with esophageal and gastric varices (band ligation and sclerotherapy), and in hepatocellular carcinoma. Liver transplantation is considered in the small proportion of children with decompensated advanced liver disease ($<$1% of indication) [41].

SCREENING AND DIAGNOSIS

Acute and chronic HCV infection is diagnosed through the recognition of HCV RNA. The sensitivity of the lower limit of the HCV RNA method should be less than 15 IU/mL. Also, HCV antibodies are detected by enzyme immunoassay in HCV infection except in early acute hepatitis C and in profoundly immunosuppressed patients. HCV antibodies detection persists after disappearance of HCV RNA following spontaneous or treatment-induced viral clearance [42,43].

In the two large Italian studies (194 and 332 children), alanine transferase (ALT) levels were persistently elevated in 42% to 45% of patients, normal or normalized in 8% to 23% and intermittently abnormal in 35% to 41% [30,37]. In children, long-term monitoring after viral clearance is essential as there is still a high risk of liver cancer. A well-defined interval for monitoring is not known, but every 6-12 months is probably reasonable to assess ALT levels and clinical status.

Studies showed that coexistence of positive liver kidney microsomal (LKM) antibodies in HCV pa-

tients was associated with increased rates of fibrosis (Ishak score >3 in 27%) [38]. LKM1 markers were recognized in 6-10% of children with chronic HCV infection.

HISTOLOGIC FINDINGS

A liver biopsy is needed for precise assessment of the organ status during chronic hepatitis and usually pertain mild hepatic lesions during childhood. Comparable results have been achieved using non-invasive tests and scans (Fibro-Test, Acti-Test and Elastography fibroscan) in children with hepatitis C. A fibroscan score of 8.2 in hepatitis C is equivalent to a fibrosis stage 1-2 or (F1- F2) [44].

In patients with chronic HCV infection, there is accumulation of inflammatory cells in the portal tracts. Subsequently, inflammation of the margins of the parenchyma and liver tracts will lead to liver cell necrosis and fibrosis. Initially, mild fibrosis is present in the portal tracts and parenchyma and as severity progresses, bridging between the portal tracts and hepatic veins are established. Finally, fibrosis leads to cirrhosis, and thus the fibrous septa separate the liver into nodules [45].

Histology activity index (HAI), was first noted by Knodell et al. [46] in 1981, and was called the Knodell score. A revised form was described by other international scholars led by Ishak (a pathologist who worked with Knodell in his original score) and produced the Ishak score [47], which addressed the critics for the Knodell score. For grading, numbers were assigned to the severity of the necroinflammatory features (interface hepatitis, confluent necrosis, parenchymal injury and portal inflammation) and added together to reach a score from 0 to 18. For staging, numbers from 0 to 4 can be added into the Knodell score; while in the Ishak score, the staging is reported separately and ranges from 0 to 6.

In the study of the Italian and the Spanish hepatitis C children, the HAI was found to be low in the majority of patients, with a mean value of 3.6 (range from 0-11) [30,37]. Normal liver histology or minimal lesions was found in 14 out of 80 cases, chronic hepatitis with a low activity in 48 cases and high activity in 17 cases. Those children, that were diagnosed to be with high activity chronic hepatitis, were significantly older (12 years) than children with low-activity chronic hepatitis or minimal liver lesions (8 years). Only one of the 80 children (1.3%) had cirrhosis.

Fibrosis scores were significantly correlated to duration of disease, portal inflammation and interface hepatitis [48]. In a later report with additional children (total of 112 cases) fibrosis was assessed by a simpler system called Metavir score [49], which grade the activity into mild (A1), moderate (A2) or marked (A3). They observed strong correlation between the stage of fibrosis and the age of the children at biopsy and the duration of their infection. The patients whose infection lasted less and more than 10 years showed big difference. Using a linear progression analysis, they 'estimated' that the mean rate of fibrosis progression was 0.227 ± 0.372 Metavir units per year, with a median of 0.142, and thus a mean time of 28 years would elapse before development of cirrhosis. However, the rate of 'observed' fibrosis progression per year averaged 0.112 ± 0.14 in the 13 subjects who were re-biopsied (seven had increased and six unchanged scores).

Serum ALT levels showed no correlation to HAI. A report on 121 children with compensated HCV disease, who were recruited from several American centers, has concluded that children with normal ALT levels are likely to encounter significant hepatic inflammation as those with high ALT levels. Five patients (4.2%) showed in their biopsies bridging fibrosis while two (1.7%) revealed cirrhosis. There was a highly significant correlation between hepatic inflammation and fibrosis [50,51].

STANDARD TREATMENT HEPATITIS C INFECTION

For acute HCV infection in children, no definite treatment is indicated. Early intervention using antiviral therapy is not yet defined specially that the patients are mostly missed during this stage [52].

The main objective for treatment of chronic HCV is to convert detected HCV viremia to below the detection limit of the quantitative polymerase chain reaction (PCR) (30-50 IU/mL). Once this negativity is achieved, continuation of treatment must be sustained long enough to ensure eradication of the infection in the liver and the extrahepatic sites. This will minimize the complications of cirrhosis, reduce the risk of hepatocellular carcinoma and the other extrahepatic complications if present [52].

Children with chronic HCV infection are usually asymptomatic and rarely develop severe liver damage. Therefore, the benefits from current therapies, pegylated-interferon (PEG-IFN) plus ribavirin, must be weighed against their adverse effects. This combined treatment offers a 50-90% chance of clearing HCV infection according to several studies and on different HCV genotype [53-56]. Recent DAA drugs which are well established for adults have not yet been approved for children and young adults below 18 years.

Two forms of PEG-IFN have been developed and currently used, the peginterferon alfa-2b (PEG-IFN-α-2b) and the peginterferon alpha-2a (PEG-IFN-α-2a). USA Food and Drug Adminstration (FDA) approved in 2008 the use of peginterferon alfa-2b and ribavirin regimen in children with HCV aged 3 years and older, and then in 2011 approval of peginterferon alfa-2a in combination with ribavirin in children aged 5 years and older was instituted [57].

The addition of polyethylene glycol moiety to IFN-α confers an extended serum half-life compared with native IFN-α, allows once-weekly dosing and significantly improved the response rates. PEG-IFN-α-2a is using a large (40 kD) branched polyethylene glycol molecule, while PEG-IFN-α-2b is using a smaller (12 kD) linear molecule. PEG-IFN-α-2b in a dose of 60 micrograms/m^2 subcutaneously weekly (maximum dose 1.5 micrograms/kg) is recommended to children over 3 years of age, while PEG-IFN-α-2a in a dose of 180 micrograms/1.73 m^2 once per week (maximum dose 180 micrograms) is recommended only for children over 5 years. Either of them are given in combination with ribavirin in a dose of 15 mg/kg/day orally with food, divided into 2 doses. Ribavirin is a guanosine analog. The recommended duration of therapy for genotype 1 and 4 is 48 weeks; while for genotype 2 or 3 is only 24 weeks [58].

Common terminology was introduced to define HCV response of treatment. 'Rapid viral response' means that viremia turned undetectable in week 4 of treatment, 'early viral response' means that the HCV RNA became negative by week 12, and 'end of treatment response' means that viremia were negative at the end of treatment. 'Sustained virologic response (SVR)' defines that HCV RNA remained undetectable 24 weeks after end of treatment (i.e., resolution of infection), 'partial response' means that at 24 weeks of treatment there was a decline in serum HCV RNA level but is still detectable, while 'nonresponse' is mentioned when there is detectable serum HCV RNA at 24 weeks of treatment without any significant decrease in the levels. 'Relapse' means that serum HCV RNA reappeared after an end-of-treatment response had been achieved. PEG-IFN is a more convenient drug than the conventional IFN because of the weekly administration. The use of PEG-IFN-α-2b or PEG-IFN-α-2a in the combined treatment achieved similar rates of SVR in several controlled studies [59-63].

The proportions and the qualities of adverse events of PEG-IFN have been similar to the ones recognized with the conventional non-pegylated IFN though they were limited to the one weekly versus the three doses weekly. To avoid marked neutropenia encountered with the PEG-IFN, the dose can be temporarily decreased if the neutrophil count declines below 1-1.25$\times 10^9$ cells/mL. PEG-IFN are transiently withheld if the neutrophil counts are below 0.75-1.00$\times 10^9$ cells/mL; and reinstituted once the neutrophil counts normalize [60-63].

Clearance of ribavirin is through the kidneys, so the dose should be decreased in patients with low creatinine clearance and completely avoided in renal failure. Hemolytic anemia, being the main toxic effect of ribavirin, if this anemia is recognized during treatment, ribavirin dose should be temporarily reduced or discontinued [60-63].

Presence of several comorbid medical conditions

in the form of moderate or severe depression, psychiatric conditions, and seizures which compromise the drugs response mandates exclusion from the combined treatment. Patients testing positive for autoimmunity markers are enrolled if other features of autoimmune hepatitis are not present. Adolescents should practice birth control during combined therapy and for 6 months after treatment cessation. Pregnancy testing is advised for all girls in the child-bearing period before commencing treatment [64].

The response to treatment has been linked to recent observations in at least 2 genetic polymorphisms of the IL28B receptor in adults [65]. Polymorphisms near the IL28B gene, encoding IFN-λ-3, have been used as a predictive value to treatment response which showed an approximately twofold change. This predictive value of IL28B receptor polymorphisms should be further studied in children infected with HCV.

As mentioned earlier, the viral genotype should be recognized in order to predict the response to the therapy and to design the duration of therapy. Different HCV genotypes exhibit different responsiveness to treatment. Genotypes 2 and 3 are more responsive, with cure rates of 83-100% of all patients treated for 24 weeks. In the case of the genotypes 1 and 4, the overall SVR rate is around 50%, for the longer 48 weeks of therapy. The need for a liver biopsy to assess the disease activity in pediatric age is controversial as treatment decisions should not rely on the histological findings, but it is still the only method to identify severe cases [66].

Several studies have been published with data on efficacy and adverse effects of the combined treatment of PEG-IFN plus ribavirin in children. A study conducted in a center in Spain; recruited 30 children (24 naive) [67], while another trial was carried out in several centers in Germany, and recruited 61 children, 51 were naive [68].

In both studies the duration of treatment was 24 or 48 weeks for genotype 2 or 3 infected children, and for 48 weeks in the case of genotype 1 or 4 infected children. In the Spanish study, the patients' ages were between 3.5-16 years, 69% of them were due to vertical transmission, 86.6% was of genotype 1 (27 children), and the baseline viral load was >5 $\log_{10}$ IU/mL in 66.6% of cases. SVR was attained in 15 of the 30 patients (50%). All three (100%) patients with HCV genotype 3 attained SVR, while only 12 (44%) out of 27 with HCV genotype 1 attained SVR. The one patient with HCV genotype 4 showed no response. All the 15 children with the SVR remained HCV RNA-negative at periodic follow-up visits for 3 years with normal liver function levels [67,68].

In the German study, the children aged 2 to17 years of age; vertical transmission was condemned in 40.3% of the infections and 75.8% of the patients carried genotype 1 HCV [68]. All 13 individuals with genotype 2 or 3 attained SVR, irrespective of the duration of treatment (i.e., 24 or 48 weeks) ($p<$ 0.0003), while 22 out of the 46 patients (47.8%) with genotype 1 showed SVR. One of the two patients (50%) with genotype 4 had SVR.

Several adverse effects were encountered. The emergence of thyroid antibodies and thyroid-stimulating hormone elevation during treatment was evident in both studies [68,69]. Transient flu-like symptoms with variable intensity, including moderate fever, were observed during the earlier weeks of treatment in all patients in all age groups, but regressed during the second 6 months. Ribavirin induced hemolysis was recognized but not to the extent that required adjustment in the drug dosage. Increase in the reticulocyte levels during therapy was observed but returned to normal levels thereafter. School performance was not grossly affected. Transient changes in character or mood have been observed in 15-30% of the children, but severe psychological involvement was not encountered [67,68]. Depression should be looked for in adolescents, as previous studies reported suicidal inclination and attempts during treatment with conventional IFN-α plus ribavirin [69]. The children experienced growth faltering during the treatment period by a mean of 1.6 cm compared to the average growth for age and gender. Growth velocity returned to normal in the 6-month period post-treatment,

however no catch-up growth was observed in the short term [70].

Several studies in Egypt were carried on children 3-18 years of age. They were suffering from chronic HCV genotype 4 and showed SVR ranging between 23.9% to 62%. There were 46 children in the first study and 140 children in the second study. All patients received a weekly subcutaneous injection of PEG-IFN-alpha-2a with a daily oral ribavirin dose for 48 weeks. The parameters related to a better response were the male gender, the short duration of infection, the low viral load, the mild hepatic activity, and the mild hepatic fibrosis. Only mild reversible adverse effects were encountered and the treatments were well tolerated by the children [53, & personal communication].

FUTURE THERAPIES FOR CHILDREN WITH HEPATITIS C INFECTION

There are several revolutionary therapies growing rapidly for chronic HCV infection. The introduction of the DAA agents and combination drug therapies is an important landmark in the treatment of HCV in adults and will likely similarly change the management of children in few years. There are currently no published studies using DAA agents in children. The early research on protease inhibitors, telaprevir were started in the pediatric patients, but were quickly stopped with the rapid rise of more effective and less toxic agents [57].

DAA therapies have been instituted and implemented, for adults in the US, Canada, European Union, Japan, Russia and Egypt, and were expanded recently outside North America to Asia and the Middle East. The designated companies have signed licensing agreements with several governments to facilitate easier and cheaper access to these therapies. These drugs most likely will be approved soon for use in children due to their high safety and efficacy [57].

Current HCV therapies target viral proteins involved in HCV replication and assembly such as the NS3/NS4A protease, NS5B RNA–dependent RNA polymerase, and the NS5A replication complex component. Combination therapies employ multiple DAAs that target different stages of the HCV life cycle. They can block cellular entry of the virus neutralizing antibody, SR-B1 inhibitor, inhibit or interfere with protein synthesis NS3/4a: protease inhibitor, inhibit or interfere with genome replication NS5B polymerase nucleos(t)ide and nonnucleoside analogs, NS5A inhibitors, NS4B, miR-122, cyclophilins, HMG CoA, siRNAs, inhibit or interfere with assembly and secretion of glucosidases, LDL pathway blockers, and other mechanisms such as use of immunomodulators, antifibrotic agents, and new interferons who are undergoing IFN-a–based treatment (2B; CIII) [71].

In started in 2011, two first-wave, first generation telaprevir and boceprevir were licensed for HCV genotype 1 infection. Both drugs are protease inhibitors that target the HCV NS3-4A serine protease. They must be given in combination with pegylated interferon α (PegIFN-α) and ribavirin. This combination therapy achieved higher SVR rates than the PegIFN-α and ribavirin dual therapy alone, reaching 65% to 75%. As soon as other, more efficacious and better tolerated options were available, this triple therapy was discontinued due to their costs and their triple side effects [52,72].

Three other new HCV DAAs were licensed in Europe in 2014. The revolutionary sofosbuvir, a pangenotypic nucleotide analogue inhibitor of HCV RNA-dependent RNA polymerase, was the first to be introduced in January. The second being simeprevir, a NS3-4A protease inhibitor active against genotypes 1 and 4 has been approved in May 2014. Daclatasvir, a pangenotypic NS5A inhibitor, was present in August 2014. Each of these three DAAs in combination with PegIFN-α and ribavirin, produced SVR rates of 60-100% [52].

Later they were employed as IFN-free combinations and with advanced fibrosis (score F3 or F4 widely used across Europe in late 2014, especially in patients). The combination of sofosbuvir and ribavirin was used for patients with HCV genotypes 2 (12 weeks) or 3 (24 weeks). They achieved SVR rates of 80-95%. In a small-sized Phase II study a combina-

tion of sofosbuvir and simeprevir, with or without ribavirin, was used in genotype 1 patients and yielded SVR rates of 93-100%. In US trials in patients with genotype 1 infection, The TRIO and the Target studies showed 82% SVR12 and 89% SVR4 respectively. The combination of sofosbuvir and daclatasvir, with or without ribavirin were extensively used in Europe in genotype 1 cases with advanced liver disease and reported very high SVR rates of ABT-450, ABT-493, ABT-530, ombitasvir, dasabuvir, vedroprevir, grazoprevir, elbasvir, GS-5816, GS-9857, and many others evolving currently [73-89].

The results of the safety and efficacy studies of DAA combinations in adults encouraged scholars to evaluate the pharmacokinetics (PK) of sofosbuvir and ledipasvir/sofosbuvir on an adolescent population with HCV infection. They were 12-17 years of age adolescents, weighing ≥45 kg at baseline. They received either sofosbuvir 400 mg once daily plus weight-based ribavirin for 7 days (n=10), or ledipasvir/sofosbuvir 90 mg/400 mg once daily for 10 days (n=10). Upon completion of evaluation, patients were continued on sofosbuvir plus ribavirin for 12 or 24 weeks or ledipasvir/sofosbuvir for 12 weeks. On Day 7 for sofosbuvir plus ribavirin or Day 10 for ledipasvir/sofosbuvir, Intensive PK assessments were calculated to compare sofosbuvir, GS-331007 (predominant circulating metabolite) and ledipasvir PK parameters. The safety profile was assessed periodically. Study results demonstrated comparable PK parameters and safety profile between the adult and adolescent populations. There were adverse events in five adolescents of the sofosbuvir plus ribavirin group and 3 adolescents of the ledipasvir/sofosbuvir group [90].

The high efficacy of combined therapy in adolescents warrants its application in younger children. However, more in-depth studies are needed, with further investigation of the factors implicated in the development of adverse events.

PREVENTION OF HEPATITIS C INFECTION

The most important field for the prevention of HCV infection in children would be the prevention of perinatal and parenteral transmission. With the implementation of the DAA therapies that target HCV, it may be possible soon that these regimens will be used specially in the perinatal period.

In April 2014, World Health Organization (WHO) launched guidelines for the screening, care and treatment of persons with hepatitis C. This included two aspects, the first being the primary prevention for healthy individuals and the second being for people already infected with the HCV.

The primary prevention for healthy individuals included firstly basic concepts in the form of washing of hands and using of gloves; also the safe handling and disposing of sharp objects and garbage; governing safe activities for individuals who are using injections by sterilizing equipment; thorough examination of blood and its products for hepatitis C; educating health personnels; and promoting the continuous use of condoms [23].

For people already infected with the HCV, WHO recommended secondary prevention through educating and counseling the patients and their care takers on options for care and management; immunizing with the hepatitis A and B vaccines to prevent coinfection and aggravation of liver status; the early management using optimal therapies if appropriate; and continuous monitoring for early diagnosis of chronic liver disease [23]. Several attempts for production of hepatitis C vaccine are in the pipeline, but not yet reaching the production phases.

In conclusion, there are areas of focus for new lines of research in pediatric HCV-related disease that can be addressed in the near future. These include research of drugs focused on vertical transmission that can effectively eliminate the majority of the pediatric cases and on development of an HCV vaccine that have the potential to significantly reduce transmission. Also, there is a need for early inclusion of children in studies of PK and safety in accordance with the adult studies, thus allowing early access to effective therapies. Research on the effect of infection on the stigmatization of infected children and their families need to be addressed. Also,

studies on chronic infection outcome and treatment and their effect on growth and cognitive behavior of the children to assist the decision makers on the timing of therapy.

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