Review Article

The Role of Direct-acting Antivirals in the Treatment of Children with Chronic Hepatitis C

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Abstract

In the United States, chronic infection with the hepatitis C virus (HCV) affects an estimated 0.1–2% of the pediatric population, who are consequently at risk for major complications, including cirrhosis, hepatocellular carcinoma, and death. The current standard of treatment for chronic hepatitis C (CHC) in children is pegylated-interferon-alpha (PEG-IFN) in combination with ribavirin. PEG-IFN/ribavirin therapy is approved for children ages 3 and older; however, it is often held from use until adulthood because of its extensive list of potential side effects and high likelihood of causing adverse symptoms. While CHC is usually indolent in children and adolescents, immediately treating and curbing the spread of HCV before adulthood is important, as there can be transmission to other individuals via sexual activity and infected females can later vertically transmit the infection during pregnancy, the latter representing the most common means of transmission for children in the United States. The recent development of direct-acting antivirals has shown promising results in clinical trials for use in children and has dramatically increased the rates of sustained virological response in adults while improving side effect profiles as compared to interferon-based treatments. Given the usually indolent course of CHC in children, significant side effects of the currently-approved PEG-IFN/ribavirin therapy, and likely availability of all-oral interferon-free regimens for children within a few years, deferring treatment in clinically-stable children with CHC in anticipation of upcoming superior treatment modalities may be justified.

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Introduction

Hepatitis C virus (HCV) is an RNA virus which affects >180 million people worldwide,[1] with global seroprevalence of antibodies to HCV increasing from 2.3% in 1990 to 2.8% in 2005.[2] In North America, the overall prevalence of HCV antibody positivity is estimated to be about 1–1.5%, with 0.17% in 6–11 year-olds and 0.39% in 12–19 year-olds. HCV has a high propensity for chronic infection and is the leading cause of chronic infectious hepatitis in children in industrialized countries.[3] Depending on population and risk factors, chronic HCV infection (CHC) is estimated to affect 0.1–2% of children in the United States (US).[4] CHC is defined as evidence of active viral infection with detectable HCV RNA for at least 6 months, with the implication of ongoing liver injury.[1] In the US, this translates to CHC afflicting 23,000–46,000 children,[5] who are subsequently at risk for its complications, including cirrhosis, liver cancer, and death.[6]

Virology

HCV is a single-stranded, positive-sense RNA virus belonging to the *Flaviviridae* family and hepacivirus genus. There are six genotypes, numbered 1–6, with 100 subtypes, denoted by lower-case letters.[7] Predominance of genotypes vary geographically, with the most common (genotype 1) having worldwide distribution but predominance in North America (HCV 1a) and Europe (HCV 1b). Genotypes 2 and 3 also have worldwide distributions, while genotype 4 is predominantly in North Africa and the Middle East, genotype 5 is in South Africa, and genotype 6 is in Asia.[3] The specific genotype of the virus has important implications for treatment, as genotypes 1 and 4 are more difficult to cure with interferon (IFN)-containing regimens as compared to genotypes 2 and 3, though overall genotype 3 is considered the most challenging to treat.[8] Furthermore, the viral RNA polymerase is highly error prone, leading to the rapid development of multiple 'quasispecies' within a single individual. It is speculated that these quasispecies, and their interactions with their host, may explain the variability in the clinical course of the disease among individuals infected with HCV.[7,9]

Natural history of HCV in children

The transmission of HCV requires blood contact, and the means of transmission include blood, blood products, organ transplantation, tissue penetration with infected objects (such as contaminated needles and tattooing instruments), sexual

contact, and vertical transmission from mother to child. Prior to the implementation of rigorous screening measures in 1992, most children acquired HCV from blood, blood products, or organ transplantation. Since 1992, by far the most common means of transmission has become vertical transmission,[10] and in the US, there are an estimated 7,500 new cases annually from vertical transmission.[11]

Vertical transmission occurs in 5–10% of at-risk pregnancies,[12,13] and factors which increase the risk of transmission include concomitant maternal human immunodeficiency virus (HIV) infection, high maternal HCV viral load (>600,000 IU/mL), internal monitoring of the fetus, prolonged rupture of membranes, and fetal anoxia around time of delivery.[1] Spontaneous resolution of infection can occur in early infancy, with 25–40% of infected infants clearing the infection. This phenomenon can occur in older children as well, but has been reported at far lower rates of 6–12%. Spontaneous resolution has been observed in children up to 7–8 years of age, but is much rarer after age 3.[6] The majority of children (54–86%) will go on to develop CHC.[3]

The clinical course of CHC acquired in childhood appears to be mild: most children are asymptomatic, there is no effect on growth,[14] histopathological changes usually only show minimal inflammation,[15] and hepatocellular carcinoma is rare, with two cases having been documented.[16] On the other hand, adolescents who become infected follow the adult pattern of disease.[2] However, CHC is considered a progressive disease with accumulating liver damage:[17] there is a 26-fold increase in risk of liver-related death associated with CHC acquired in childhood;[11] bridging fibrosis is reportedly present in 12% of children;[18] cirrhosis is present in 1–2% of children; decompensated cirrhosis has been documented in children between the ages of 4–11; and liver transplantation may be necessary for end-stage liver disease secondary to CHC.[16] Furthermore, hepatocellular carcinoma has been reported in adults with CHC in the absence of cirrhosis.[19]

The 10-year costs associated with pediatric HCV infection are estimated to be $199–336 million.[5] Furthermore, children with CHC experience impaired quality of life due to multiple factors, including developmental delay, learning disorders, and cognitive deficits less severe than those of attention deficit hyperactivity disorder, but still indicative of decreased executive function.[20]

Current treatment for children with CHC

Currently, the only US Food and Drug Administration (FDA)-approved therapy for CHC in children ages 3 and older is pegylated-interferon-alpha (PEG-IFN) in combination with ribavirin.[21] IFN is a cytokine that induces multiple IFN-stimulated genes, including double-stranded RNAses, inhibitors of viral protein translation, and proteins which destabilize viral messenger HCV RNA. The expression of these genes under the influence of IFN also results in the activation of natural killer cells, maturation of dendritic cells, proliferation of memory T cells, and prevention of T cell apoptosis.[22] The pegylation of IFN to large molecule polyethylene glycol results in a longer half-life, better pharmacokinetic profile, and better rate of virological response.[23,24] Ribavirin is a synthetic guanosine analogue that interferes with the synthesis of guanosine triphosphate, inhibiting the viral capping of mRNA as well as the viral RNA polymerase.[25] The addition of ribavirin to PEG-IFN improved sustained virological response (SVR) up to 30–40%, along with end-of-treatment response (ETR), in

adults and children,[26] as well as significantly decreased the relapse rate of HCV infection.[27,28]

There are two formulations of PEG-IFN which are FDA-approved for use in children with CHC. PEG-IFN-2b is dosed at 60 g/m^2/week, while PEG-IFN-2a is dosed at 180 g/1.73 m^2/week. Both options are delivered subcutaneously once weekly, and neither has been consistently demonstrated to have superiority over the other. Concurrently, children should receive ribavirin, dosed at 15 mg/kg/day per os (PO) divided twice daily. Duration of therapy depends on HCV genotype, with 48 weeks of therapy for genotypes 1 and 4, and 24 weeks for genotypes 2 and 3.[1] The efficacy of this treatment regimen also varies by genotype; a meta-analysis of 8 trials evaluating the efficacy of PEG-IFN with ribavirin found children with genotypes 1 and 4 achieved early virological response (EVR) and SVR 61% and 52% of the time, respectively. This is in contrast to children with genotypes 2 and 3, who achieved EVR and SVR 87% and 89% of the time, respectively. Overall, SVR was achieved in 58% of children, with relapse rate of 7%, and 15% of children not showing virologic response to therapy.[29]

In adults receiving PEG-IFN with ribavirin, rapid virological response (RVR) has been identified as the best predictor of SVR, and viral load <600,000 IU/mL has been found to be a positive predictor for SVR in adults with HCV genotype 1.[30] Single nucleotide polymorphisms (SNPs) around the gene for interleukin 28B (IL-28B) have been associated with different treatment results in adults,[31] and preliminary studies in children may confirm a similar result in children. Specifically, IL-28B rs12979860 CC and rs8099917 TT may be associated with higher rates of SVR in children with genotypes 1 and 4 who are treated with PEG-IFN and ribavirin.[32] Otherwise, other predictors of SVR in adults, including younger age, baseline aminotransferase levels, sex, previous treatments, and liver histology, have not been confirmed in children.[30]

While discontinuation of therapy due to adverse events is low at 4%, adverse events occur in almost all children undergoing treatment with PEG-IFN and ribavirin.[29] PEG-IFN almost universally causes constitutional symptoms, including fever, fatigue, myalgia, arthralgia, headache, nausea, and other nonspecific gastrointestinal complaints.[33] One-third of children experience bone marrow suppression (neutropenia, thrombocytopenia), as well as neuropsychiatric complications (irritability, depression, and rarely suicidal ideation).[26] PEG-IFN can also cause hypothyroidism,[34] ophthalmological complications,[35] and injection site reactions.[36] Ribavirin can cause hemolytic anemia[34] and rash.[36] Furthermore, both medications are considered teratogenic.[37] Weight loss and inhibited growth are also seen; however, most children will have compensatory weight and height gain after completion of therapy.[30]

New therapy for CHC in adults

In adults, PEG-IFN and ribavirin have been supplanted by newer therapies; specifically, small molecules known as direct-acting antivirals (DAAs) have been developed which target viral enzymes responsible for various parts of the HCV life cycle. The HCV genome encodes a single precursor polyprotein that is processed by host signal peptidases and HCV proteases into two classes of proteins: structural (core, envelope E1, E2/p7) and non-structural (NS2: protease, NS3: protease, NS4A: cofactor for NS3, NS5A: creates changes in the cellular membrane allowing for viral replication, NS5B: RNA polymerase).[38,39] DAAs target non-structural proteins,

and the current DAAs in clinical use have been classified as NS3/4A protease inhibitors, NS5A inhibitors, and NS5B polymerase inhibitors (Table 1).

NS3/4A protease inhibitors interfere with HCV polyprotein processing by targeting the shallow enzymatic groove of the HCV protease.[40] The addition of NS3/4A protease inhibitors to the traditional PEG-IFN/ribavirin therapy resulted in increased SVR rates, up to 70–80% in treatment-naïve (TN) HCV genotype 1 patients.[41,42] Unfortunately, there is a low barrier to resistance with NS3/4A protease inhibitors,[43] as well as severe side effects. Newer NS3/4A inhibitors (including grazoprevir, simeprevir, and paritaprevir which is given with ritonavir, an HIV protease inhibitor which inhibits cytochrome P3A4 to boost paritaprevir's activity), have broader genotype activity as well as improved tolerability and resistance profiles.[6] The newest NS3/4A protease inhibitor is grazoprevir, which is administered in conjunction with the NS5A inhibitor elbasvir, with or without ribavirin, and is an approved therapy for HCV genotypes 1 and 4.[44]

NS5A is an RNA-binding protein involved in modulating the cellular environment by interacting with other non-structural proteins, and is required for viral assembly.[45,46] NS5A inhibitor monotherapy results in rapid HCV RNA decline, but also rapid development of resistance;[47] thus, it is used in combination with other agents.[48] In addition, 10–15% of HCV genotype 1-infected patients will have NS5A resistance-associated variants (RAVs) at baseline, which can decrease NS5A activity by greater than 5-fold. NS5A-containing regimens can still be utilized in these patients, but with the addition of weight-based ribavirin.[44] The newest approved NS5A inhibitors

Table 1. Currently approved direct-acting antiviral agents

NS3 protease inhibitors	None currently available
NS3/4A protease inhibitors	Grazoprevir Paritaprevir Simeprevir
NS5A inhibitors	Daclatasvir Elbasvir Ledipasvir Ombitasvir Velpatasvir
NS5B non-nucleoside polymerase inhibitors	Dasabuvir
NS5B nucleoside analogue polymerase inhibitors	Sofosbuvir

include elbasvir, given with NS3/4 protease inhibitor grazoprevir, as well as velpatasvir, given with the NS5B nucleoside analogue inhibitor sofosbuvir. The latter is the first approved all-oral pan-genotypic HCV treatment regimen in the US.[49]

NS5B inhibitors interfere with viral replication by binding the NS5B RNA-dependent RNA polymerase.[25] They are classified as nucleoside analogue inhibitors (which are incorporated into the RNA chain and thus cause chain termination) or non-nucleoside inhibitors (which act on various allosteric sites to induce conformational change in the RNA polymerase).[50] NS5B non-nucleoside inhibitors have good efficacy in reduction of HCV RNA levels and have mild, well-tolerated side effects.

Table 2. Treatment options for adults with CHC without cirrhosis (listed by evidence then alphabetically)

Genotype	Recommended	Alternative
1a	Elbasvir/grazoprevir × 12 weeks (if no NS5A RAVs) (Class I, Level A) Ledipasvir/sofosbuvir × 12 weeks (Class I, Level A) Paritaprevir/ritonavir/ombitasvir with dasabuvir and ribavirin × 12 weeks (Class I, Level A) Simeprevir with sofosbuvir × 12 weeks (Class I, Level A) Sofosbuvir/velpatasvir × 12 weeks (Class I, Level A) Daclatasvir with sofosbuvir × 12 weeks (Class I, Level B)	Elbasvir/grazoprevir with ribavirin × 16 weeks (if NS5A RAVs detected) (Class IIa, Level B)
1b	Elbasvir/grazoprevir with ribavirin × 12 weeks (Class I, Level A) Ledipasvir/sofosbuvir × 12 weeks (Class I, Level A) Paritaprevir/ritonavir/ombitasvir with dasabuvir and ribavirin × 12 weeks (Class I, Level A) Simeprevir with sofosbuvir × 12 weeks (Class I, Level A) Sofosbuvir/velpatasvir × 12 weeks (Class I, Level A) Daclatasvir with sofosbuvir × 12 weeks (Class I, Level B)	N/A
2	Sofosbuvir/velpatasvir × 12 weeks (Class I, Level A)	Daclatasvir with sofosbuvir × 12 weeks (Class IIa, Level B)
3	Daclatasvir with sofosbuvir × 12 weeks (Class I, Level A) Sofosbuvir/velpatasvir × 12 weeks (Class I, Level A)	N/A
4	Paritaprevir/ritonavir/ombitasvir with dasabuvir and ribavirin × 12 weeks (Class I, Level A) Sofosbuvir/velpatasvir × 12 weeks (Class I, Level A) Elbasvir/grazoprevir × 12 weeks (Class IIa, Level B) Ledipasvir/sofosbuvir × 12 weeks (Class IIa, Level B)	N/A
5/6	Sofosbuvir/velpatasvir × 12 weeks (Class I, Level A) Ledipasvir/sofosbuvir × 12 weeks (Class IIa, Level B)	N/A

Abbreviation: RAV, resistance-associated variant.

Unfortunately, they also have a low barrier to resistance and high frequency of viral breakthrough when given as monotherapy,[51,52] and do not have broad genotype activity.[53] However, they can be effective in combination with other classes of DAAs.

NS5B nucleoside analogue inhibitors have broad genotype activity, as they target a highly conserved region among genotypes. They also have a high barrier to resistance, as mutations in the viral RNA polymerase lead to loss of function and impaired viral replication, and have fewer drug interactions compared to protease inhibitors.[25] Sofosbuvir was the first available NS5B nucleoside analogue inhibitor.[54] The current recommendations for treatment of adults with CHC are summarized in Tables 2–4.[44,55]

Some of the newest DAAs under investigation include voxilaprevir (NS3/4A protease inhibitor given with sofosbuvir and velpatasvir), glecaprevir (NS3/4A protease inhibitor) given with pibrentasvir (NS5A inhibitor), and ruzasvir (NS5A inhibitor given with investigational compound MK-3682 and grazoprevir). After the completion of four international Phase 3 trials, the combination of voxilaprevir with sofosbuvir and velpatasvir resulted in 95–97% achieving SVR at 12 weeks after treatment (SVR-12) in patients across all genotypes, and included patients who had failed other DAAs.[56–59] Glecaprevir and pibrentasvir resulted in high rates of SVR across all genotypes in five Phase 3 trials, including in patients with chronic kidney disease.[60–65] Lastly, ruzasvir with MK-3682 and grazoprevir also resulted in high rates of SVR-12 in patients with HCV genotypes 1–3 in Phase 2 trials.[66–68]

Future therapies for CHC in children

There are case reports discussing isolated usage of DAAs in the pediatric population. Sofosbuvir and simeprevir have been used in two patients, one with a stem cell transplant and one with an umbilical cord blood transplant. The first patient was a 13 year-old boy with HCV genotype 4c who underwent stem cell transplant for sickle cell disease, and thereafter his HCV RNA levels increased to 10–50 million IU/mL. He was treated with 400 mg of sofosbuvir and 150 mg of simeprevir once daily for 12 weeks, with HCV RNA becoming negative at the end of treatment, as well as at 11 and 21 weeks thereafter.[69] The second patient was a 4 year-old girl with HCV genotype 1a who underwent umbilical cord transplant for acute lymphoblastic leukemia. Upon immune recovery, she developed symptoms of acute hepatitis and was treated with 200 mg of sofosbuvir and 75 mg of simeprevir for 24 weeks. Her HCV viral loads have been tracked for 1.5 years and remain negative.[70] Lastly, ledipasvir/sofosbuvir has been used in an adolescent female with decompensated cirrhosis secondary to HCV genotype 1a, with HCV RNA being undetectable 4 months after initiation of treatment.[71]

Given the success of DAAs in treating adults with CHC, there are now multiple clinical trials evaluating DAA use in children. Thus far, two have been completed, and three are ongoing. One of the completed trials was a Phase 1/2 open-label trial examining telaprevir in combination with PEG-IFN and ribavirin in children with CHC secondary to HCV genotype 1 (Vertex Pharmaceuticals, clinicaltrials.gov, NCT01701063).

Table 3. Treatment options for adults with CHC with compensated cirrhosis (listed by evidence then alphabetically)

Genotype	Recommended	Alternative
1a	Elbasvir/grazoprevir × 12 weeks (if no NS5A RAVs) (Class I, Level A) Ledipasvir/sofosbuvir × 12 weeks (Class I, Level A) Sofosbuvir/velpatasvir × 12 weeks (Class I, Level A)	Paritaprevir/ritonavir/ombitasvir with dasabuvir and ribavirin × 24 weeks (Class I, Level A) Simeprevir with sofosbuvir with or without ribavirin × 24 weeks (if no Q80K polymorphism; Q80k reduces simeprevir efficacy) (Class II, Level B) Daclatasvir with sofosbuvir with or without ribavirin × 24 weeks (Class IIa, Level B) Elbasvir/grazoprevir with ribavirin × 16 weeks (if NS5A RAVs detected) (Class IIa, Level B)
1b	Elbasvir/grazoprevir × 12 weeks (Class I, Level A) Ledipasvir/sofosbuvir × 12 weeks (Class I, Level A) Paritaprevir/ritonavir/ombitasvir with dasabuvir × 12 weeks (Class I, Level A) Sofosbuvir/velpatasvir × 12 weeks (Class I, Level A)	Daclatasvir with sofosbuvir with or without ribavirin × 24 weeks (Class IIa, Level B) Simeprevir with sofosbuvir with or without ribavirin × 24 weeks (Class IIa, Level B)
2	Sofosbuvir/velpatasvir × 12 weeks (Class I, Level A)	Daclatasvir with sofosbuvir × 16–24 weeks (Class IIa, Level B)
3	Sofosbuvir/velpatasvir × 12 weeks (Class I, Level A) Daclatasvir with sofosbuvir with or without ribavirin × 24 weeks (Class IIa, Level B)	N/A
4	Paritaprevir/ritonavir/ombitasvir with dasabuvir and ribavirin × 12 weeks (Class I, Level A) Sofosbuvir/velpatasvir × 12 weeks (Class I, Level A) Elbasvir/grazoprevir × 12 weeks (Class IIa, Level B) Ledipasvir/sofosbuvir × 12 weeks (Class IIa, Level B)	N/A
5/6	Sofosbuvir/velpatasvir × 12 weeks (Class I, Level A) Ledipasvir/sofosbuvir × 12 weeks (Class IIa, Level B)	N/A

Abbreviation: RAV, resistance-associated variant.

Table 4. Treatment options for adults with CHC and decompensated cirrhosis (listed by evidence then alphabetically)

Genotype	Patients who may/may not be transplantation candidates	Patients who are ribavirin ineligible	Patients in whom prior sofosbuvir-based treatment failed
1/4	Ledipasvir/sofosbuvir with low dose ribavirin (increase as tolerated) × 12 weeks (Class I, Level A) Sofosbuvir/velpatasvir with weight-based ribavirin × 12 weeks (Class I, Level A) Daclatasvir with sofosbuvir and low dose ribavirin (increase as tolerated) × 12 weeks (Class I, Level B)	Sofosbuvir/velpatasvir × 24 weeks (Class I, Level A) Daclatasvir with sofosbuvir × 24 weeks (Class II, Level C) Ledipasvir/sofosbuvir × 24 weeks (Class II, Level C)	Ledipasvir/sofosbuvir with low dose ribavirin (increase as tolerated) × 24 weeks (Class II, Level C) Sofosbuvir/velpatasvir with weight-based ribavirin × 24 weeks (Class II, Level C)
2/3	Sofosbuvir/velpatasvir with weight-based ribavirin × 12 weeks (Class I, Level A) Daclatasvir with sofosbuvir and low dose ribavirin (increase as tolerated) × 12 weeks (Class II, Level B)	N/A	N/A

Of the 42 children enrolled, 69% of children ages 12–17, 89.5% of children ages 6–11, and 40% of children ages 3–5 achieved SVR. This study was terminated early after the completion of the Phase 1 portion, and telaprevir was withdrawn from the US market in October 2015. Similarly, a second study evaluating boceprevir with PEG-IFN and ribavirin in children ages 3–17 with CHC secondary to HCV genotype 1 was withdrawn (Merck Sharp & Dohme, clinicaltrials.gov, NCT01590225), as it was anticipated that newer, all-oral interferon-free regimens would replace this regimen by the time the study ended.[6]

Currently, there are three active, multicenter, all-oral interferon-free clinical trials examining DAA use in children. Two of these are Phase 2 trials, and one is Phase 3. The Phase 3 trial is recruiting children ages 3–17 with HCV genotypes 1a, 1b, and 4, with and without compensated cirrhosis. All are treated with ombitasvir/paritaprevir+ritonavir, and those with genotypes 1a also receive dasabuvir and ribavirin. Children with genotype 1b receive dasabuvir without ribavirin, and children with genotype 4 receive ribavirin without dasabuvir. Duration of therapy will be 12 weeks, with the exception of children with genotype 1a with cirrhosis; they will receive 24 weeks of therapy. This is a three-part study evaluating pharmacokinetics (part 1), safety/efficacy (part 2), and long-term follow-up (part 3). Primary outcome measures for parts 2 and 3 include percentage of participants with SVR-12, percentage who relapse after SVR, and percentage who develop new HCV infection after achieving SVR. The estimated study completion date is January 2023 (AbbVie, clinicaltrials.gov, NCT02486406).

The two Phase 2 trials are recruiting children ages 3–17, and both are being conducted by Gilead Sciences. One study is recruiting children with genotypes 2 and 3 (Gilead, clinicaltrials.gov, NCT02175758), the other genotypes 1, 3, 4, 5, 6 (Gilead, clinicaltrials.gov, NCT02249182). For the former, participants are divided into ages 3–5, 6–11, and 12–17, with 50 children between ages 3–11 and 50 between ages 12–17. All are treated with sofosbuvir and ribavirin. Dosing is 200 mg in ages 6–11, which is based off of pharmacokinetic data from adults as well as from a lead-in group of patients in the 6–11 age group.[72] Those in the 12–17 year-old group received the adult dose of 400 mg of sofosbuvir, as pharmacokinetic results from the lead-in patients in that group

demonstrated comparable plasma exposure and safety profiles with adult dosing of sofosbuvir and ribavirin in adolescents as in adults.[73] Completion of pharmacokinetic lead-in studies for ages 3–5 is pending. Duration of therapy is 12 weeks with genotype 2, and 24 weeks with genotype 3. Primary outcome measures for the treatment phase is incidence of any adverse event resulting in discontinuation of study drugs, with SVR-12 as a secondary outcome measure. The estimated study completion date is April 2018, though dosing for the 12–17 age range has been completed. Thirteen patients had HCV genotype 2, while 37 had genotype 3. Among those with genotype 2, 62% were male, 85% were white, mean age was 15 years, mean body mass index (BMI) was 21 kg/m^2 (range, 16–28 kg/m^2), mean HCV RNA was 5.9 log$_{10}$ IU/mL, and all were TN. Among those with genotype 3, 57% were male, 92% were white, mean age was 15 years, mean BMI was 23 kg/m^2 (range, 16–32 kg/m^2), mean HCV RNA was 6.2 log$_{10}$ IU/mL, and 76% were TN. Overall SVR-12 was 98%, with all 13 genotype 2 patients achieving SVR-12, and 36 out of 37 genotype 3 achieving SVR-12. No serious adverse events or treatment discontinuation occurred. Among those with genotype 2, the most common adverse events were headache (23%), nausea (23%), abdominal pain (15%), and diarrhea (15%). Among those with genotype 3, the most common adverse events were headache (24%), nausea (24%), asthenia (14%), and dizziness (11%).[74]

For the latter study, participants are divided into ages 3–11 and 12–17, with 100 children in each group. All are treated with ledipasvir/sofosbuvir, and as with the other study, dosing in the younger group will be based on pharmacokinetic lead-in results, while those in the older group receive the adult dose of ledipasvir/sofosbuvir at 90 mg/400 mg. For ages 6–11, dosing has been determined to be ledipasvir/sofosbuvir at 45 mg/200 mg, with dosing for ages 3–5 to be determined. No serious adverse events occurred in children ages 6–11 during pharmacokinetic studies.[72] Genotype 1, 4, 5, and 6 TN participants with and without cirrhosis, along with treatment-experienced (TE) participants without cirrhosis, will receive treatment for 12 weeks; for TE participants with cirrhosis, the duration will be 12–24 weeks, based on genotype and country location of study site. For genotype 3, only TE participants will be recruited, and all will receive ledipasvir/sofosbuvir along with ribavirin for 24 weeks. Of note genotype 3

participants will only be recruited from the United Kingdom; participants with the other genotypes will be recruited from the US, United Kingdom, Australia, and New Zealand. The primary outcome measure for the treatment phase is whether any adverse events resulted in the discontinuation of study drugs; SVR-12 is one of the secondary outcome measures. The estimated study completion date is April 2018. Pharmacokinetic data from the lead-in subjects for ages 6–11 and 12–17 are available,[72,73] with studies for ages 3–5 pending. The adult fixed-dose of ledipasvir/sofosbuvir resulted in similar plasma exposure of ledipasvir, sofosbuvir, and GS-331007 (the inactive metabolite of sofosbuvir) in adolescents as in adults, thus the adult dose was used for this age group.[75] Similarly, giving half the adult fixed-dose of ledipasvir/sofosbuvir, 45 mg/200 mg, to children ages 6–11 resulted in comparable plasma exposure of ledipasvir, sofobuvir, and GS-331007 as in adults, without any severe adverse events or laboratory abnormalities.[72]

Results in 100 adolescents with HCV genotype 1 treated with ledipasvir/sofosbuvir are available.[75] The mean age was 15 years, 37% were male, 90% were white, mean weight was 61 kg (range, 33–126 kg), mean baseline HCV RNA log_{10} IU/mL was 6.0 (range, 4.7–7.0 log_{10} IU/mL), with 55% having HCV RNA >800,000 IU/mL, 81% with genotype 1a, 80% as TN, 1% with cirrhosis, and 84% infected via vertical transmission. Ledipasvir/sofosbuvir was well tolerated, without grade 3 or 4 adverse events (severe or life-threatening adverse events), and there was no treatment discontinuation due to adverse events. The most common reported adverse events were headache (27%), diarrhea (14%), fatigue (13%), nausea (12%), cough (10%), and vomiting (10%). There were 9 participants with transient grade 3–4 laboratory abnormalities, which later resolved. Furthermore, 98 out of 100 participants (78 out of 80 TN, 20 out of 20 TE) achieved SVR-12. The remaining two participants were lost to follow-up, but both remained HCV negative at the last visit they attended. One was negative by week 2, with last follow-up at week 4, and the other negative by week 8, with last follow-up at week 12. There were no virologic failures, and the only patient with cirrhosis achieved SVR-12.[75] Quality of life indicators also significantly improved both during and after achieving SVR.[76] Post-treatment follow-up to evaluate SVR at 24 weeks is ongoing.[77]

Conclusions

The development of DAAs has dramatically increased the rates of SVR in adults while improving the side effect profile, and clinical trials for DAA use in children have been promising. Long-term safety and efficacy data in children is needed, but given the usually indolent course of CHC in children, significant side effects of the currently approved PEG-IFN/ribavirin therapy, and the anticipated approval of ledipasvir/sofosbuvir and sofosbuvir with ribavirin for adolescents potentially as early as 2017, deferring treatment in clinically-stable children with CHC in anticipation of upcoming superior treatment modalities may be justified.

Conflict of interest

Author contributions

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