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HEPATITIS C (H VARGAS AND S FLAMM, SECTION EDITORS)

State of the Art HCV Treatment in Children

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Abstract

Purpose of Review Hepatitis C infection is a global issue with an estimated 5 million children with active HCV infection worldwide. The advent of oral direct-acting antiviral (DAA) regimens has revolutionized treatment in adults with excellent efficacy and tolerability. There are limited data and few approved therapies in children. The aim of this review is to discuss the currently approved regimens for children and the recently reported results of clinical trials of DAA in children.

Recent Findings DAA regimens are currently approved only for children ≥ 12 years. For most children < 12 years, it is recommended that HCV therapy be deferred until patients are eligible for oral DAA therapies. For treatment-naïve adolescents with HCV genotype 1, 4, 5, or 6, treatment with ledipasvir/sofosbuvir for 12 weeks has been reported to have sustained virologic response at 12 weeks of 98%. For treatment-naïve adolescents with genotype 2 or 3 HCV, sofosbuvir- ribavirin combination therapy (12 weeks for genotype 2 and 24 weeks for genotype 3) has been reported to have SVR12 of 100% and 97%, respectively. There are promising, recently published studies showing excellent SVR12 rates for ombitasvir/paritaprevir/ritonavir ± dasabuvir ± ribavirin in adolescents with HCV genotype 1 or 4, and sofosbuvir/daclatasvir in children/adolescents with HCV genotype 4. Finally, ledipasvir/sofosbuvir ± ribavirin for children age 6–12 years with genotypes 1, 3, 4, 5, and 6 treated for either 12 or 24 weeks is reported to have an SVR12 rate of 99%.

Summary HCV treatment in children is rapidly evolving. There are now highly effective all-oral, interferon-free regimens for children ≥ 12 years. Clinical trials are on-going for adolescents and children < 12 years with a variety of pangenotypic ribavirin-free regimens, with anticipated approvals in the near future.

Keywords Pediatric · Children · Hepatitis C · HCV · Treatment · Direct-acting antiviral

Introduction

There are approximately 115 million people infected with hepatitis C virus (HCV) worldwide [1]. Although children are a small percentage of this group, it is estimated that 11 million children younger than 15 years have had HCV. Of these, 5 million are viremic. In the USA, although the prevalence of anti-HCV was estimated at 0.2% in children ages 6–12 and 0.4% in those age 12–19 years in reviews from the late 1990s [2–4], the rate of new HCV infection is rising in young adults, including women of child-bearing age [5, 6], and pediatric infections are expected to increase.

Chronic HCV infection generally progresses slowly and serious consequences (cirrhosis and hepatocellular carcinoma) are rare in children, since advanced liver disease is uncommon until more than 30 years after infection [7, 8]. Children who are infected perinatally have spontaneous clearance rates of 20–45% within the first 3 years of life [3, 7–13].

Diagnosis

Diagnosis of HCV infection in children 18 months or older usually begins with detection of HCV antibody. A positive or equivocal test should be followed by HCV ribonucleic acid (RNA) testing. If positive, HCV infection is confirmed. In infants less than 18 months, serum HCV

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antibody reflects maternal antibodies, so is not a reliable test for the diagnosis.

When HCV infection is confirmed, additional evaluation is warranted after age 3. HCV genotyping helps guide the selection and duration of therapy. Testing for coinfection with hepatitis B virus is also indicated. Additionally, patients should be screened for hepatitis A immunity.

Disease severity should be assessed clinically. For most children, a liver biopsy is not necessary and does not influence treatment decisions. A liver biopsy may be considered if there is comorbid liver disease or there is concern for advanced liver disease, since some regimens require longer treatment in cirrhotics. There are recent papers supporting the utility of transient elastography in the evaluation of chronic liver disease in children [14, 15].

Monitoring

In patients with chronic HCV infection, disease severity should be assessed, and monitored serially if treatment is not offered.

- Serum aminotransferases—Although serum aminotransferases are not strictly reflective of HCV disease severity, serial monitoring with alanine aminotransferase levels every 6–12 months is recommended. In children with other medical comorbidities, like HIV coinfection, clinicians should consider more frequent lab testing. It is important to note that in a report of 121 treatment-naïve children with HCV infection, a third of patients had normal aminotransferase levels despite biopsy proven evidence of inflammation [16].
- HCV RNA—Serial HCV RNA testing is not recommended for most children. However, if the ALT becomes normal for more than 1 year, clinicians can consider retesting the RNA to assess for spontaneous clearance. Also, if the patient becomes treatment eligible, retesting HCV RNA is reasonable to confirm active HCV.
- Malignancy—Hepatocellular carcinoma is associated with HCV in the setting of cirrhosis, coinfection with HBV, and history of childhood leukemia or other malignancy [17, 18]. In patients with these risk factors, surveillance with liver ultrasonography and serum alpha fetoprotein levels are recommended every 6 months [19••]. Continued monitoring for HCC is recommended in successfully treated hepatitis C in adult patients with cirrhosis; there are no data regarding this strategy in pediatrics, but careful follow-up of these patients is probably judicious

Treatment

Acute Infection

Acute HCV infection is rarely recognized in children except in the setting of IV drug use in adolescents. Fulminant hepatitis is also rare. There are no data or recommendations regarding treatment of acute HCV in children. It is prudent to assess patients with acute HCV for 6–8 weeks to assess for spontaneous clearance. For those patients who remain viremic, treatment can be considered, using regimens efficacious for chronic infection.

Chronic Infection

The treatment of chronic hepatitis has been rapidly evolving since the advent of direct-acting antiviral agents (DAAs). The DAAs have made the previous regimens involving combination therapy with interferon and ribavirin much less desirable, since outcomes are better, side effects are substantially fewer, and treatment duration is shorter. In adults, the all-oral, interferon-free DAA regimens are now standard of care because of their consistently superior sustained virologic response (SVR) rates, short therapy durations, and tolerability. In addition to similarly poor efficacy in children, interferon-based regimens have the added adverse effect of temporary growth impairment. The development and Food and Drug Administration (FDA) approval of DAA regimens for adults and adolescents 12 years and older has been a transformative moment in clinical care. By selecting the appropriate regimen for the genotype, cirrhosis status, and treatment history, the DAA combination regimens offer oral, interferon-free regimens with high efficacy rates. Clinical trials of newer regimens for all children and established regimens for children age 3–11 years are currently ongoing, with expectations for availability in the next couple of years.

In the USA, treatment of children with chronic HCV infection who are eligible for DAA regimens in their age group is recommended regardless of disease severity [19••]. Treatment for children 3–11 years of age should be deferred until regimens without interferon are available. For all children, extra-intestinal manifestations of HCV infection (cryoglobulinemia, rash, glomerulonephritis) and/or advanced fibrosis warrant consideration of early antiviral therapy.

Currently Approved Treatment Regimens

A. Children < 12 Years

There are to date no FDA-approved DAA regimens for children < 12 years of age. Since most children with HCV have slowly progressive disease, it is recommended that treatment

for children < 12 years be deferred until they are eligible for a DAA treatment regimen by regulatory approval or enrolling in a clinical trial. Until then, patients should be monitored with serial aminotransferases and assessment for advancing liver disease. The uncommon pediatric patients with cirrhosis should be monitored periodically for complications, such as hepatocellular carcinoma, but this is very rare during the childhood years.

If patients are in resource-limited areas (where oral DAA regimens may not be available for some time), clinicians could consider treatment for HCV genotype 2 or 3 with the combination of pegylated interferon and ribavirin, given that the efficacy rate is reasonable (80–100% SVR). Unfortunately, the efficacy of pegylated interferon/ribavirin for genotypes 1 and 4 is quite poor (40–50% SVR), so awaiting significantly more effective DAA is preferred.

B. Children ≥ 12 Years

Children 12 years and older and who weigh at least 35 kg are eligible for some DAA regimens (Fig. 1) [19••, 20]. These regimens are first-line for children without cirrhosis and in those with compensated cirrhosis.

Genotype 1, 4, 5, or 6

The approved regimen for adolescents with genotype 1 HCV who are treatment naïve without cirrhosis or with compensated cirrhosis, or treatment-experienced without cirrhosis, is ledipasvir-sofosbuvir for 12 weeks (Table 1). Patients with genotype 1 who are treatment-experienced with compensated cirrhosis can be treated with ledipasvir-sofosbuvir for 24 weeks. For patients with HCV genotype 4, 5, or 6 who are treatment-naïve or treatment-experienced without cirrhosis or with compensated cirrhosis, the recommendation is ledipasvir-sofosbuvir for 12 weeks.

Genotype 2 or 3

The currently approved option in adolescents is sofosbuvir-ribavirin for 12 weeks (GT 2) or 24 weeks (GT3) (Tables 2 and 3). This regimen includes the potential adverse effects of ribavirin, although it is generally well tolerated in children.

Alternate DAA regimens may be available in clinical trials or outside the USA.

Recommendations for Patients Initiating Treatment

- HBV coinfection should be assessed with HBV core antibody prior to treatment. There are reports of HBV reactivation in adults with HCV/HBV coinfection.
- Pregnancy should be excluded. To date, none of the regimens have been approved for use in pregnant women. Ribavirin is contraindicated in pregnant women and the male sexual partners of pregnant women. For female patients of childbearing age, contraception should be addressed prior to, during, and 6 months after the completion of ribavirin therapy.
- Drug toxicity should be monitored. Although drug toxicity with DAA combinations is uncommon, basic laboratory testing (complete blood count, creatinine, liver enzymes) at week 4 is recommended [20]. Subsequent lab testing should be done as clinically indicated.
- Treatment efficacy is determined by undetectable HCV RNA at 12 weeks after therapy completion.

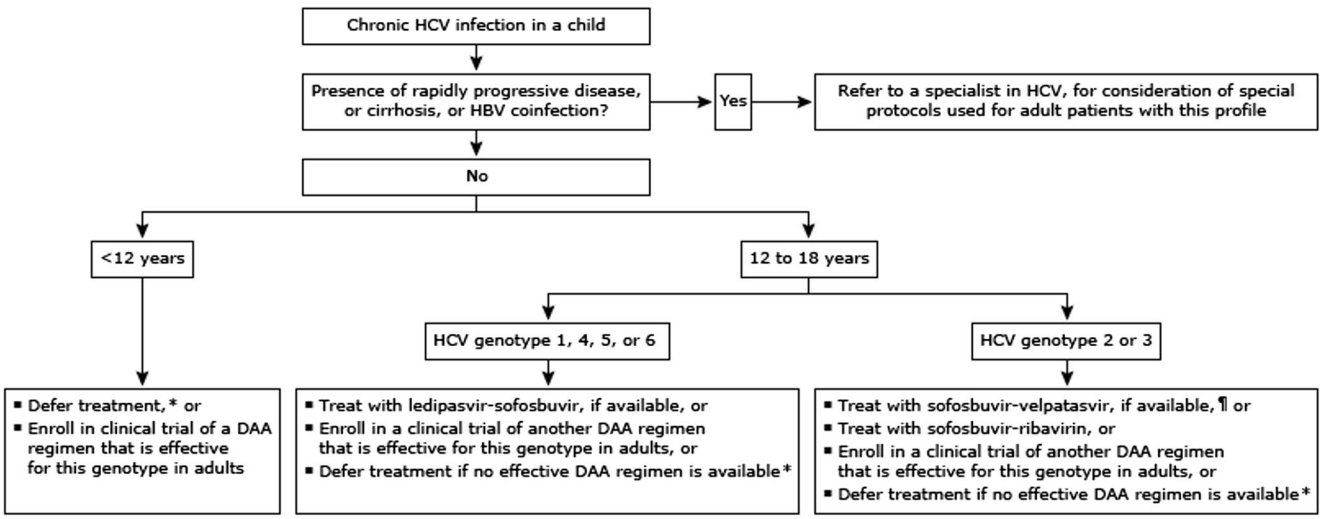

Fig. 1 Algorithm for chronic HCV infection treatment in children. Reproduced with permission from Jonas MM. Hepatitis C virus infection in children. In: UpToDate Post TW (Ed), UpToDate, Waltham, MA (Accessed on 12/15/2018.) Copyright © 2018 UpToDate, Inc. For more information visit www.uptodate.com

Table 1 Recommendations for chronic HCV genotypes 1, 4, 5, and 6 in children ≥ 12 years. Treatment-experiences are patients who have failed a previous interferon regimen (± ribavirin). Compensated cirrhosis refers to patients with a Child-Pugh Class A designation

Genotype	Patient ≥ 12 years	Medication	Duration
1	-Treatment-naïve without cirrhosis -Treatment-naïve with compensated cirrhosis -Treatment-experienced without cirrhosis	Ledipasvir 90 mg/ Sofosbuvir 400 mg Once daily	12 weeks
1	-Treatment-experienced with compensated cirrhosis	Ledipasvir 90 mg/ Sofosbuvir 400 mg Once daily	24 weeks
4, 5, 6	-Treatment-naïve or treatment-experienced without cirrhosis -Treatment-naïve or treatment-experienced with compensated cirrhosis	Ledipasvir 90 mg/ Sofosbuvir 400 mg Once daily	12 weeks

Special Situations Additional consideration must be given to patients with co-infection with hepatitis B, HIV, and/or failed prior therapy. Unfortunately, there are few data on treatment of adolescents in these situations. Clinicians may want to consider regimens available for adults in similar situations. In adults with HIV co-infection, the HCV treatment should be undertaken first, as HIV coinfection is a factor in more rapid progression of liver disease [20]. Caution and monitoring are recommended in patients with HBV coinfection as reactivation during DAA therapy has been reported. Active HBV infection should be treated at the same time or prior to starting HCV DAA therapy [20]. Patients with low/undetectable HBV DNA levels can be considered for either prophylactic treatment for HBV or monitoring with monthly HBV-DNA testing.

Clinical Trials

Genotypes 1 and 4

A phase 2, multicenter open-label, fixed-dose, combination regimen of fixed-dose ledipasvir 90 mg and sofosbuvir 400 mg once daily for 12 weeks was conducted in 100 adolescents (age 12–17 years) [21•]. Eighty percent of patients were HCV treatment-naïve, and 84% patients were infected via perinatal transmission. One patient was known to have cirrhosis, 42 patients did not have cirrhosis, and in 57 patients, the cirrhosis status was not known. Ninety-eight percent of patients achieved SVR at 12 weeks (SVR12) and none had virologic failure. The two patients who did not reach SVR were lost to follow-up. No serious adverse events were reported and the most commonly reported side effects were headache (27%), diarrhea (14%), and fatigue (13%). These data contributed to the approval of this regimen in adolescents.

A recent communication reported the first data from an ongoing, open-labeled, phase 2/3 study of ombitasvir/paritaprevir/ritonavir (OBV/PTV/r) regimen with or without dasabuvir (DSV) and ± ribavirin (RBV) in 38 adolescents, aged 12–17 years, and weight ≥ 45 kg with HCV genotype 1 or 4 who were treatment naïve or interferon experienced [22]. Part 1 is a phase 2 study involving the adult dose/formulation of OBV/PTV/r (25 mg/150 mg/100 mg once daily) + DSV (250 mg, twice daily) ± RBV (weight-based dosing) for 12 weeks for genotype 1 HCV without cirrhosis. Part 2 is a phase 3 study designed to look at OBV/PTV/r ± DSV ± RBV for 12 or 24 weeks in genotype 1 or 4 without cirrhosis or with compensated cirrhosis. Of the 38 patients enrolled, 42% had genotype 1a, 40% genotype 1b, and 18% genotype 4. One

Table 2 Recommendations for chronic HCV genotypes 2 and 3 in children ≥ 12 years. Treatment-experiences are patients who have failed a previous interferon regimen (± ribavirin). Compensated cirrhosis refers to patients with a Child-Pugh Class A designation

Genotype	Patient ≥ 12 years	Medication	Duration
2	-Treatment-naïve or treatment-experienced without cirrhosis -Treatment-naïve or treatment-experiences with compensated cirrhosis	Sofosbuvir (400 mg) once daily And Ribavirin (weight-based dosing) twice daily	12 weeks
3	-Treatment-naïve or treatment-experienced without cirrhosis -Treatment-naïve or treatment-experiences with compensated cirrhosis	Sofosbuvir (400 mg) once daily And Ribavirin (weight-based dosing) twice daily	24 weeks

Table 3 Ribavirin dosing for use in sofosbuvir combination therapy in patients ≥ 12 years

Weight (kg)	Total daily Ribavirin dose (divided into two doses)
< 47	15 mg/kg/day
47–49	600 mg/day
50–65	800 mg/day
66–80	1000 mg/day
> 80	1200 mg/day

patient had cirrhosis. Twelve patients were included in part 1 and 26 patients in part 2. The SVR12 rate was 100% overall. No severe lab abnormalities or serious adverse events were reported. The most common side effects reported were headache (21%), fatigue (18%), nasopharyngitis (13%), pruritus (13%), and upper respiratory infection (11%).

Genotype 4

A multicenter, open-label study of 144 adolescents with genotype 4 was conducted using a regimen of ledipasvir 90 mg and sofosbuvir 400 mg once daily for 12 weeks [23]. SVR at 12 weeks was reached by 99% patients. No serious adverse events occurred; the most common side effect was headache in 20%. This data contributed to the approval of this regimen in adolescents. Similar findings were reported in another observational study of ledipasvir mg/sofosbuvir once daily for 12 weeks in 40 adolescents aged 12 to < 18 years, weighing > 35 kg [24]. SVR12 was 100%. The most common side effects reported were asthenia (52.5%) and headache (47.5%).

A recent publication reported the safety and efficacy of the combination of sofosbuvir and daclatasvir in children age 8–18 years, weighing at least 17 kg, with genotype 4 HCV [25]. Forty treatment-naïve children with compensated liver disease were enrolled. Patients received sofosbuvir (SOF) (400 mg/day for patients weight > 45 kg, 200 mg/day for weight 17–45 kg) and daclatasvir (DCV) (60 mg/day for patients weight > 45 kg, 30 mg/day for weight 17–45 kg) for 12 weeks. Forty-five percent of patients were < 12 years of age. Of these patients, 72.5% had genotype 4 and 27.5% had mixed genotype 4 and 1 infections. SVR12 was 97.5% and SVR 24 was 95%, respectively, on an intention to treat basis, while it was 100% and 100% for the patients who completed the study protocol.

There are no clinical trial data for genotype 5 or 6 HCV infections in children.

Genotypes 2 and 3

The combination of sofosbuvir 400 mg once daily and weight-based ribavirin was studied in 12 adolescents (age 12–17) with genotype 2 HCV for 12 weeks and in 24 adolescents with genotype 3 HCV for 24 weeks [26•]. Eighty-three percent of patients were treatment-naïve. Forty percent of patients did not have cirrhosis; in 60%, the cirrhosis status was not known. SVR12 was achieved in 100% of genotype 2 and 97% of genotype 3 infections. The 1 patient who did not achieve SVR12 was lost to follow-up but known to have achieved SVR4. The most common side effects were nausea (27%) and headache (23%). These data contributed to the approval of this regimen in adolescents.

All Genotypes

The most recent published study reported the safety and efficacy of ledipasvir 45 mg-sofosbuvir 200 mg ± ribavirin in children age 6 to < 12 years [27]. This was an open-label study using two fixed-dose combination tablets 22.5/100 mg once daily. Ninety-seven percent of children were perinatally infected and 78% were treatment-naïve. There were 92 children in the cohort: 88 with HCV GT 1 (77 1a), 2 with GT3, and 2 with GT 4. Two patients had cirrhosis, while the fibrosis status was unknown in 55 patients. All patients were assigned to ledipasvir/sofosbuvir for 12 weeks. Those patients who were interferon-experienced with cirrhosis and genotype 1 were treated for 24 weeks. Patients with genotype 3, interferon-experienced patients with/without cirrhosis were given ledipasvir-sofosbuvir with ribavirin for 24 weeks. SVR12 was 99%. One cirrhotic patient with GT 1a HCV relapsed 4 weeks after completing 12 weeks of therapy. The most common side effects reported were headache and pyrexia. One patient was reported to have three serious adverse events (tooth abscess, abdominal pain, gastroenteritis) which were thought not to be related to treatment.

At The Liver Meeting in 2018, an open-label, multicenter phase 2/3 trial of glecaprevir/pibrentasvir in children was presented [28]. Part 1 of the study involved adolescents age 12–17 who received the adult formulation of fixed dose glecaprevir 300 mg/ pibrentasvir 120 mg. Forty-four treatment-naïve, non-cirrhotic patients were treated for 8 weeks and 3 treatment-experienced, non-cirrhotic patients were treated for 12 weeks. There were 37 patients with GT1, 3 patients with GT2, 4 patients with GT3, and 3 patients with GT4. The SVR12 for the overall population, individual genotypes, and HIV-co-infected patients was 100%. No patients experienced a serious adverse event. The most common adverse events reported were nasopharyngitis, upper respiratory tract infection, and headache.

Conclusions

Hepatitis C infection in children is a worldwide problem, and approximately 5 million children worldwide are infected. HCV infection is typically a slowly progressive disease

throughout the childhood years but can cause cirrhosis during childhood. HCV is associated with significant morbidity from advanced liver disease and malignancy as duration of infection increases. Direct-acting antiviral therapies have significantly shortened the duration of therapy and significantly improved outcomes in adults. Highly effective DAA therapies are now approved for adolescents and have been shown to have excellent safety and tolerability (Tables 1, 2, and 3). Several clinical trials are investigating pangenotypic ribavirin-free DAA regimens for adolescents and for younger children, increasing the anticipation that these therapies will be approved for use in the near future. All children with chronic HCV infection should be treated when these regimens are available, regardless of liver disease severity.

Compliance with Ethical Standards

Conflict of Interest Maureen M. Jonas reports grants from Gilead Sciences, grants from AbbVie, grants from Merck, grants from Bristol Myers-Squibb, grants from Roche, and personal fees from Gilead Sciences, outside the submitted work. Christine K. Lee received research support in the form of transient elastography hardware from Echosens; no other support was given.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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