Treatment of hepatitis C virus chronic infection in children: is there a cure in sight or are we far away from the goal?

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Abstract

Infection with hepatitis C virus is a global health problem; in Mexico, approximately 2% of the population is infected. In children, data on prevalence are variable according to the age group, but 0.1-2% of children are estimated to have chronic infection with hepatitis C virus, the main way of transmission of which is perinatal. Currently, there are direct-acting antiviral agents approved in adults that offer a sustained viral response rate higher than 95%; however, in children there are still only few studies confirming their safety and effectiveness. Although we are still far from the goal, we are rapidly advancing towards an optimal curative treatment also for pediatric patients.

KEY WORDS: Hepatitis C virus. Direct-acting antiviral agents. Sustained viral response.

Basic concepts

Hepatitis C virus (HCV) Infection is a global public health problem that affects between 170 and 210 million people in the world, with between three and four million being infected annually.¹ In Mexico approximately 1 to 2.5 % of adult population is infected.^{2,3} Little has been studied in Mexico on the prevalence of HCV infection in children; however, in other countries such as the United States, there is an estimate of 240,000 children with anti-HCV antibodies, with a prevalence of 0.2 % for children under 12 years of age and 0.4 % for children between 12 and 19 years of age.⁴⁻⁶ In Europe, a prevalence of 1.5 % is estimated in children under 15 years of age and 2.3 % in those older than 15 years.⁷ In other studies, prevalence is as high as 5.8 %, and in countries such as Egypt, a prevalence of up to 6% has been reported.^{1,5,8} In a study conducted in Mexico in children with acute hepatitis, a prevalence of 2 % was found for HCV infection.⁹ The transmission routes in children are

mainly perinatal and transfusional.^{5,6} Pediatric patients frequently develop chronic infection, but with a less aggressive evolution than in adults.^{10,11}

Chronic hepatitis C virus infection in children

Hepatitis C virus (HCV) is an RNA virus of the *Flaviviridae* family. There are six genotypes, which differ from each other in their amino acid sequence in 31 to 34 %.^{1,12} The virus is made up of nine proteins, including RNA polymerase, and its genome was cloned for the first time in 1989. The most common genotype is genotype 1, followed by genotypes 2 and 3.^{6,12} The other genotypes are rare in the United States and Mexico: genotype 4 is more common in Northern Africa and the Middle East, genotype 5 in South Africa and genotype 6 in Asia.⁵

Liver disease caused by HCV infection is divided in acute hepatitis C and chronic hepatitis C (CHC). Chronic HCV infection is defined by the presence of HCV RNA for more than six months.⁶

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Neonatal HCV infection is documented in children by the presence of HCV RNA in months one through six of life, and must be distinguished from transient viremia due to perinatal transmission, which is defined when RNA is found in newborns within the first five days of life or in umbilical cord blood, which is not relevant.⁶

Infection transmission and spontaneous resolution in children

The main source of infection in pediatric patients since HCV screening in blood products is perinatal.¹³ An estimate of 60,000 HCV-infected children are born annually in the world; however, prophylactic caesarean section is not recommended to prevent HCV transmission, except in women with high risk transmission factors, such as coinfection with the human immunodeficiency virus.¹ The placenta and certain innate immune response factors have been described to possibly have a protective or eradicating role in neonates.⁶

Given that perinatal transmission is the most common route for HCV infection in children, the main risk factors for it have been studied, as well as factors that do not appear to impact on the transmission rate, which are shown in Table 1.¹⁴⁻¹⁹

IgG HCV antibodies (anti-HCV) cross the placenta; therefore, they are not reliable until 18 months of age. Anti-HCV antibodies have been reported to disappear at 15 months of age in uninfected children; however, in infected children they persist throughout the follow-up.¹⁶ HCV viral load should be measured preferably after two months of age and, if positive, be checked at 12 months of age.⁶

There are guidelines for monitoring and evaluating neonates born to HCV-positive mothers. The guidelines published by Resti et al.²⁰ refer that perinatal transmission occurs almost exclusively in mothers with a positive viral load and increases the probability of higher viral load. In any case, children born to anti-HCV-positive mothers with negative viral load should be assessed with alanine aminotransferase (ALT) and viral load at between 18 and 24 months of age; if the result is normal, follow-up is to be discontinued. Neonates born to mothers with positive viral load should be evaluated at two to three months with HCV viral load and ALT; if they test positive, testing should be repeated at 12 months, and if negative, it should be repeated: if they have elevated ALT, at between six and 12 months of age, and if they have normal ALT, at between 18 and 24 months of age.^{19,20}

Table 1. Risk factors for perinatal transmission

Risk factors for perinatal transmission	<ul style="list-style-type: none"> – Maternal viral load (> 600,000 IU/mL). – Maternal coinfection with human immunodeficiency virus. – Prolonged time between rupture of membranes and delivery (> 6 hours). – Amniocentesis or perinatal monitoring invasive studies. – Maternal active drug addiction. – Eroded or fissured nipple with presence of maternal blood.
Factors that do not influence on the incidence of transmission	<ul style="list-style-type: none"> – Genotype. – Maternal coinfection with hepatitis B virus. – Type of birth (delivery or cesarean section). – Maternal age. – Gestational age at birth. – Breastfeeding (intact nipple)

Table 2. Predictive factors of spontaneous cure

Predictors of spontaneous cure	<ul style="list-style-type: none"> – ALT elevation – < 3 years – Genotype 3 – IL28B r12979860 polymorphism
Unlikely spontaneous cure	<ul style="list-style-type: none"> – Eight years of age – Coinfection with human immunodeficiency virus or hepatitis B virus – Childhood obesity?

HCV infection spontaneous resolution in children is defined as the presence of HCV antibodies, but with negative viral load found in two different samples at least six months apart from each other.⁶ According to the study by Abdel-Hady et al.,²¹ this occurs in 17 to 27 % of patients whose source of transmission was transfusion and only in 9 % of those in whom it was perinatal transmission. However, Rerksupphol et al. found that both transmission forms have the same rate of spontaneous resolution.²² A study conducted by the European Pediatric Hepatitis C Virus Infection Network found that 17 % had spontaneous resolution of the infection and that one third of pediatric patients developed cirrhosis or hepatocellular carcinoma after 20 years' evolution.¹⁴

The highest rate of spontaneous cure is reached within the first two to three years of age;⁵ however, 54 to 86 % of children develop CHC.¹² Spontaneous resolution has been described in children younger than seven or eight years; however, some studies indicate that it is rare for children older than three years to have spontaneous resolution.^{12,23} Predictive factors of spontaneous resolution have been described^{5,6} (Table 2).

Although this viral load clearance has been described as a "cure", cases of viremia recurrence

have recently been reported, and these children should therefore continue on follow up.⁵

Biopsy and noninvasive markers for children

Several studies have been carried out to validate the use of noninvasive markers of fibrosis in children. El-Shabrawi et al. conducted a study in 50 patients aged between 2 and 18 years with chronic HCV infection; they found high correlation between Fibrotest® and Actitest® (Biopredictive) and METAVIR histological score, which was useful to rule out advanced fibrosis.²⁴ Flores Calderón et al. assessed the use of Fibrotest and the AST-platelet ratio index (APRI) in 68 Mexican children, in comparison with METAVIR histological score; they found that these noninvasive fibrosis evaluation methods are reliable to identify advanced fibrosis stages (F3-F4), and thus they can be used in fibrosis evaluation follow-up in pediatric patients.²⁵

Other studies have shown that transient elastography is a useful method to assess the stage of liver fibrosis in children.^{26,27} However, although it is promising as a noninvasive marker of fibrosis in children, Lewindon et al. found that the results when measuring hepatic stiffness values are not reliable in children younger than two years of age, in addition that inter-current diseases can modify the measurement.²⁸ Similarly, invalid measurements with this method have been described to be higher in children younger than six years, and their interpretation should therefore be cautious.²⁹

Another non-invasive method for evaluating liver fibrosis that has been studied in children is supersonic shear wave elastography. Several studies describe the usefulness of supersonic shear wave elastography in children: Franchi-Abella et al. and Dhyani et al. found that this method is useful for assessing fibrosis even at early stages (F1-F2).^{30,31}

Different non-invasive methods for assessing fibrosis (transient elastography, Fibrotest, AST-to-platelet ratio index, four factor-based fibrosis index, supersonic shear wave elastography and acoustic radiation force impulse imaging) have been evaluated in children in various pathologies, even after transplantation, and have demonstrated their usefulness for initial assessment and follow-up; however, they do not always replace liver biopsy,³²⁻³⁹ which remains the gold standard for prognosis and diagnosis of many liver diseases, although non-invasive fibrosis markers that

have been shown to be useful for pediatric patients can be used for follow-up and initial assessment.^{40,41}

Quality of life in children with chronic hepatitis C virus infection

Extrahepatic CHC manifestations have been described in children (including cognitive impairment, impaired learning and delayed cognitive development), which affect their quality of life and school performance.^{1,6}

In Australia, Nydegger et al. conducted a study to assess the quality of life of children with HCV infection acquired within the first year of life; they found that despite being clinically “asymptomatic”, these children had lower quality of life, as well as a reduction in physical and mental activity.⁴²

In another study carried out by Rodríguez et al., where the impact of HCV infection was sought in children and their caregivers, a higher level of stress was found in the family sphere, which might be associated with cognitive alterations in the children.⁴³

Disease evolution, cirrhosis and hepatocarcinoma in children

CHC evolution in children who acquired the infection during childhood appears to be slow, with the majority of children remaining “asymptomatic” and without significant growth alteration.⁴⁴ Although CHC evolution is slow in children, accelerating factors, including obesity, coinfection with hepatitis B virus or human immunodeficiency virus, transfusions and cancer, have been described.⁶ Even though children exhibit a slower progression of liver disease, CHC-secondary liver cirrhosis has been reported in children since four years of age.^{12,45,46}

There are few cases of liver transplantation in children due to CHC-associated cirrhosis; however, cases of cirrhosis and hepatocellular carcinoma secondary to CHC have been described in children, as well as the presence of extrahepatic CHC manifestations, including glomerulonephritis and cognitive alterations.⁶ On the other hand, adolescents who acquire the infection exhibit the same evolution as adults.⁴⁷

In 2009, González Peralta et al. published two clinical cases of adolescent patients with hepatocellular carcinoma secondary to CHC. The first one was a 13-year-old girl (AFP = 2740 ng/mL and two lesions, of 4 and 6 cm) and the second one was a 14-year old boy (AFP = 76.6 ng/mL and one 1.5-cm lesion).⁴⁸

Table 3. Controlled trials of pegIFN treatment for chronic hepatitis C in children

Study	Type of study	Patients (n)	Age (years)	Transmission (%)	VL (IU/mL)	ALT (%)	Treatment	Genotype (%)	Duration (weeks)	EVR (%)	SVR (%)	Relapse (%)
Wirth et al. ⁶³ (2005)	Non-randomized	61	2-17 (mean 10.6)	28 Parenteral (45) 25 Vertical (40.3) 9 Unknown (14.6)	0.32-62 × 10 ⁵ (average 6.3)	≤ 30 IU/mL: 36 (58) > 30 IU/mL: 26 (42)	pegIFN alfa-2b (1.5 µg/kg/w) RBV (15 mg/kg/d)	G1: 46 G2-G3: 13 G4: 2	G1 and G4: 48 G2 and G3: 24 (5) and 48 (8)	38 (61)	58	3 (5)
Pawlowska et al. ⁶⁹ (2010)	Non-randomized	53 Native: 29 (55) Previous Tx: 24 (45)	8-17	0 Perinatal (0) 3 Transfusion (5) 28 Nosocomial (53) 9 Surgery (16)	21: < 500 000 29: > 500 000	Average 45.8±24.3 IU/mL	pegIFN alfa-2b (1.5 µg/kg/w) + RBV (15 mg/kg/d)	G1: 27 (50) G3: 2 (4) G4: 24 (46)	G1, 4: 48 G3: 24	26 (49)	26 (49)	9 (17)
Sokal et al. ⁶⁴ (2010)	Non-randomized	65	6-17	30 Perinatal (46) 15 Transfusion (23) 6 Medical procedure (9) 14 Unknown (21)	23: < 500 000 42: > 500 000	≤ 30 IU/mL: 30 (46) > 30 IU/mL: 35 (54)	pegIFN alfa-2a (100 µg/m ² /w) RBV (15 mg/kg/d)	G1: 45 (69) G2: 2 (3) G3: 16 (25) G4: 1 (1.5) G5: 1 (1.5)	G2, 3: 24 G1, 4-6: 48	G2, 3: 83 G1, 4-6: 57	G2, 3: 94% G1, 4-6: 57% SVR: 66%	0
Wirth et al. ⁶⁵ (2010)	Non-randomized	107	3-17 (3-11: 67 12-17: 40)	75 Perinatal (70), 12 Transfusion (11), 20 Other (19)	< 600,000 IU/mL: 58 (54), ≥ 600,000 IU/mL: 45 (42)	Normal: 63 (59%) Abnormal 44 (41%)	pegIFN alfa-2b (60 µg/m ² /w) RBV (15 mg/kg/d)	G1: 72 (67) G2: 15 (14) G3: 15 (14) G4: 5 (5)	G2, 3: 24 G1, 4(3 high VL): 48	73 (68)	70 (65) G1: 53 %, G2/3: 93 %, G4: 80 %	9 (8)
Ali et al. ⁷⁰ (2010)	Non-randomized	12	14-17	2 Vertical (17), 2 IV drugs (17), 2 Dental procedure (17), 1 Transfusion (8), 5 Unknown (42)	0.23-1.8 × 10 ⁶	91 (34-194) IU/mL	pegIFN alfa-2b (1.5 µg/kg/w) + RBV (15 mg/kg/d)	G: 4	48	10 (83)	9 (75)	1 (8)
Schwarz et al. ⁶³ (2011)	Randomized	114	5-17	A, 39 Perinatal (71), 6 Transfusion (11), 10 unknown (19) B, 47 Perinatal (80), 2 Transfusion (3), 10 Unknown (18)	A, 23 B, 13 (< 600 000) A, 32 B, 46 (≥ 600 000)	≤ 30 IU/mL: A, 23 (41) B, 20 (35) > 30 IU/mL: A, 32 (58) B, 37 (64)	A, pegIFN alfa-2a (180 µg/w) + RBV (15 mg/kg/d) (55 pts.) B, pegIFN alfa-2a (180 µg/w) + placebo (57 pts.)	G1: A, 45 B, 46 G2, 3: A, 10 B, 11	G1, 2, 3: 48	NR	A, 29 (53) B, 12 (21)	9 (16)
Wisniewska-Ligier et al. ⁷¹ (2013)	Non-randomized	79	8-18	ND	≤ 500,000 IU/mL: 42-500,000 IU/mL: 34	48.6±24.7 IU/mL	pegIFN alfa-2b (1.5 µg/kg/w) + RBV (15 mg/kg/d)	G1: 54 G4: 25	48	28/65 (43.1)	35 (44.3)	2 (2.5)

(Continued)

Table 3. Controlled trials of pegIFN treatment for chronic hepatitis C in children (Continued)

Study	Type of study	Patients (n)	Age (years)	Transmission (%)	VL (IU/mL)	ALT (%)	Treatment	Genotype (%)	Duration (weeks)	EVR (%)	SVR (%)	Relapse (%)
Rosen et al. ⁶⁸ (2013)	Randomized	30 (F: 13, M: 17)	3-18	12 Perinatal, 11 Transfusion, 1 Contaminated needle, 6 Unknown	134,000-26,200,000 copies/mL	24-283 IU/L (69.93±37.64 IU/L)	10: pegIFN alfa-2a (180 µg/m ² /w) or 20: pegIFN alfa 2b (1.5 µg/kg/w) + RBV (15 mg/kg/d)	G1: 23 G2: 3: 7	G1: 48 G2: 3: 24	22 (73)	20 (67)	11
El-Karakasy et al. ⁶⁶ (2016)	Non-randomized	66	3-17	ND	ND	ND	pegIFN alfa 2b (60 µg/m ² /w) RBV (15 mg/kg/d)	G: 4	48	ND	28 (42)	ND
Suzuki et al. ⁷² (2016)	Randomized	102 (IL28B CC 53 %)	3-18	Perinatal A: 14/B: 75, Transfusion A: 2/B: 7, Unknown A: 2/B: 2	< 5log IU/mL: 7, > 5log IU/mL: 95	< 30 IU/L: A: 8/B: 38 > 30 IU/mL: A: 10/B: 46	A. 18 Monotherapy: pegIFN alfa 2b (1.5 µg/kg/w) B. 84 Combination pegIFN alfa 2b (1.5 µg/kg/w) + RBV (15 mg/kg/d)	G1: 45 G2: 57	48	A: 15 (83) B: 63 (75)	A: 15 (83) B: 63 (75)	NR

VL = viral load, ALT = alanine aminotransferase, SVR = sustained viral response, pegIFN = pegylated interferon, RBV = ribavirin.

Although the prevalence of this neoplasm in pediatric patients with CHC is low, they should undergo hepatocellular carcinoma screening; however, the frequency at which it should be carried out is unknown.⁴⁹⁻⁵¹

Current treatments for chronic hepatitis C virus infection in children

Prior to the use of direct-acting antivirals (DAA), the conventional regimen used for the treatment of CHC in children older than three years⁵² was with pegylated interferon (pegIFN) and ribavirin (RBV) and although this is no longer the treatment of choice, its use continues due to the cost, availability and lack of approval of most DAAs in children.⁵³⁻⁵⁵

The treatment with pegIFN and RBV is administered for 24 to 48 weeks (depending on the HCV genotype). There are two different types of pegIFN and either of the two forms can be used. Dosing is weekly by subcutaneous injection and based on the body surface area: 180 µg/1.73 m²/week of pegIFN2a and 60 µg/m²/week of pegIFN2b, in association with orally administered RBV and whose dose is calculated by body weight at 15 mg/kg/day and is administered divided in two daily doses.

Treatment duration depends on the HCV genotype: 48 weeks for genotypes 1, 4, 5 and 6, and 24 weeks for genotypes 2 and 3.⁶ However, with this treatment, sustained viral response (SVR) is approximately 50%, which varies according to the studies and the genotype, with 36 to 50 % being observed for genotype 1 and 84 to 100 % for genotypes 2 and 3.⁵³⁻⁵⁶ In addition to a low SVR, these drugs have important adverse effects, including flu-like symptoms, myalgia, arthralgia, hypothyroidism,⁵⁷ ophthalmological complications (in 2 to 3 % of patients, mainly ischemic retinopathy and uveitis),⁵⁸ growth alterations, bone marrow suppression (anemia, neutropenia and thrombocytopenia)⁵⁹ and neuropsychiatric alterations (depression, emotional lability, irritability, agitation, aggressiveness, anxiety), among others. Of the 107 patients aged 3 to 17 years in a clinical trial of pegIFN alpha 2b plus RBV, a severe inhibition of the growth rate (percentile < 3) was observed in 70 % of patients. Of those who experienced severe growth inhibition, 20% showed an inhibited growth rate (percentile < 3), which persisted six months after treatment conclusion^{43,48,53-56,59-72} (Table 3).

IL28B polymorphisms have been described as predictors of response to the treatment with pegIFN plus RBV in children, with the CC polymorphism being

Table 4. Controlled trials and clinical cases of DAA treatment for chronic hepatitis C in children and adolescents

Study	Type of study	Patients (n)	Age (years)	Transmission (%)	VL (IU/mL)	ALT (%)	Treatment	Genotype (%)	Duration (weeks)	EVR (%)	SVR (%)	Relapse (%)
Fischer et al. ⁷⁶ (2016)	Case report	1	13	Transfusion	14 000 000	780 IU/mL	Sofosbuvir 400 mg/d + simeprevir 150 mg/d	4	12	Yes	Yes	No
Thomas et al. ⁷⁷ (2016)	Case report	1	4	Transfusion, Umbilical cord blood	31 200 000	139 IU/mL	Sofosbuvir 400 mg/d + simeprevir 150 mg/d	1a	24	Yes	Yes	No
Smith et al. ⁷⁸ (2017)	Case report	1 (cirrhosis)	14	Vertical	868 814	51	Sofosbuvir 400 mg/d + ledipasvir 90 mg/d	1a	12	Yes	Yes	No
Wirth et al. ⁷⁵ (2017)	Non-randomized	52	12-17	38 Vertical (73), 5 Transfusion (9.6), 1 Intravenous drug use (2), 1 Surgery (2), 9 Unknown (17)	≥ 800 000 IU/mL: 34	37	Sofosbuvir 400 mg/d + RBV 15 mg/kg/d	G2: 13 G3: 39	G2: 12 G3: 24	52 (100)	51 (98)	0
Balistreri et al. ⁷⁴ (2016)	Non-randomized	100 (80 naïve)	12-17	84 Perinatal (84), 5 Drug addiction (5), 2 Transfusion (2), 2 Contact with infected person (2), 7 Unknown (7)	≥ 800 000 IU/mL: 55	53	Ledipasvir 90 mg/d + sofosbuvir 400 mg/d	G1	12	NS	98 (98) 2 NC (2)	0
Wirth et al. ⁸⁰ (2017)	Non-randomized	52 (treatment naïve: 43, previous treatment: 9)	12-17	38 Perinatal (73), 5 Transfusion (10), 1 Drug addiction (2), 1 Surgery (2), 9 Unknown (17)	6.1 log IU/mL ≥ 800,000 IU/mL: 34 IL28B (CC: 19, CT: 30, TT: 3)	54	Sofosbuvir 400 mg+RBV (weight-based)	G2 (13)-G3 (39) G2: 6 G2b: 5 G2a/2c: 2 G3: 1 G3a: 38	12 (G2) 24 (G3)	G2: 13 (100) G3: 39 (100)	G2: 13 (100) G3: 38 (97)	0

DAAs = direct acting antivirals, VL = viral load, ALT = alanine aminotransferase, SVR = sustained viral response, RBV = ribavirin, NC = did not complete the study, NS = not specified.

Table 5. Ongoing controlled studies with DAAs for children and adolescents with chronic hepatitis C

Study	Patients (n)	Age (years)	Genotype	Drug	Sponsor	Phase	Termination
NCT02486406 ⁸²	74 Without cirrhosis or with compensated cirrhosis	3-17	1 and 4 (PCR>1,000 IU/mL)	Ombitasvir/paritaprevir/ritonavir/dasabuvir	Abbvie	3	Inclusion until 2019 Results 2023
NCT03080415 ⁸³	40 Treatment naïve	8-18	4	Sofosbuvir/daclatasvir	Yassin Abdelghaffar Charity Center for Liver Disease and Research	3	June 2018
NCT02249182 ⁸⁴	200	3-17	1,3-6	Sofosbuvir/ledipasvir	Gilead	2	April 2018
NCT03022981 ⁸⁵	200	3-17	1-6	Sofosbuvir/velpatasvir	Gilead	2	September 2019
NCT03379506 ⁸⁶	56 Without cirrhosis or compensated cirrhosis, treatment naïve or treatment experienced with no specific DAAs	3-18	1 y 4	Elbasvir/grazoprevir	Merck Sharp & Dohme	2	March 2020
NCT02868242 ⁸⁷	40 Children with cancer on chemotherapy	12-17	1 y 4	Sofosbuvir/ledipasvir	Gilead	2	April 2019
NCT03067129 ⁸⁸	110	3-18	1-6	Glecaprevir/pibrentasvir	Abbvie	3	September 2019
NCT03487848 ⁸⁹	30	3-18	1-6	Sofosbuvir/daclatasvir	Bristol-Myers Squibb	2	April 2021

found to be a predictor of response. Similarly, in a study conducted by Zhong et al., IL28B rs12979860 polymorphism was found to be the best predictor of treatment response in children from one to six years of age.⁷³

DAAs are drugs that target enzymes of HCV life cycle, with the most important including the protease inhibitors (NS3 [not available] and NS3/4A [grazoprevir, simeprevir, paritaprevir, glecaprevir]), NS5B polymerase inhibitors (sofosbuvir and dasabuvir) and NS5A inhibitors (daclatasvir, ledipasvir, velpatasvir, ombitasvir, elbasvir, pibrentasvir). These medications are given in association, are authorized in adults and have SVR > 95 %.¹²

Studies have been conducted to assess DAAs efficacy and safety in adolescent patients. Balistreri et al. carried out a study in 100 12 to 17-year-old adolescent patients with genotype 1 HCV chronic infection. In 84% of the patients, transmission was perinatal, and 80% of patients were treatment naïve; they were given a treatment with ledipasvir (90 mg) and sofosbuvir (400 mg) for 12 weeks, with a SVR of 98 % being found, and no patient had virological relapse. Reported adverse effects included

headache, diarrhea and fatigue, in < 30 %, with no adverse effect requiring treatment discontinuation.⁷⁴ Since 2017, two antiviral combinations (ledipasvir/sofosbuvir and sofosbuvir/RBV) have been approved in Europe for children older than 12 years. The use of sofosbuvir/ledipasvir is recommended for 12 weeks (without cirrhosis) or 24 weeks (with compensated cirrhosis) for genotypes 1 and 4; and sofosbuvir (400 mg/day/RBV according to body weight) for 12 weeks for genotype 2 and 24 weeks for genotype 3.⁸¹

There are several studies conducted in adolescents to evaluate DAAs response and side effects, which are summarized in Table 4.⁷⁴⁻⁸⁰

Future expectations

Currently, there are more than eight DAAs approved in adults for the treatment of HCV with a SVR higher than 95 % and with minimal adverse effects. Despite this great advance in adults, in children from countries such as Mexico, treatment continues to be based on pegIFN and RBV, since the use of DAAs in children is still under study.⁷⁹

Recently, new pangenomic treatments were approved, with a SVR rate > 95 %: velpatasvir/sofosbuvir (treatment duration 12 weeks) in 2016 and glecaprevir with pibrentasvir (treatment duration of eight to 12 weeks) in 2017. There are ongoing studies to evaluate treatments with DAA in pediatric patients⁸²⁻⁸⁹ (Table 5). As in adults, chronic HCV infection in children is expected to be curable in the short term with the new therapeutic lines, which in addition have fewer adverse effects.

References

- El-Shabrawi MH, Kamal NM. Burden of pediatric hepatitis C. *World J Gastroenterol*. 2013;19(44):7880-7888.
- Burguete-García AI, Conde-González CJ, Jiménez-Méndez R, Juárez-Díaz Y, Meda-Monzón E, Torres-Poveda K, et al. Hepatitis C seroprevalence and correlation between viral load and viral genotype among primary care clients in Mexico. *Salud Publica Mex*. 2011;53:S7-S12.
- Santos-López G, Sosa-Jurado F, Vallejo-Ruiz V, Meléndez-Mena D, Reyes-Leyva J. Prevalence of hepatitis C virus in the Mexican population: a systematic review. *J Infect*. 2008;56:281-290.
- Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Intern Med*. 2006;144:705-714.
- Squires JE, Balistreri W. Hepatitis C virus infection in children and adolescents. *Hepatol Commun* 2017;1:87-98.
- Mack CL, Gonzalez-Peralta RP, Gupta N, Leung D, Narkewicz MR, Roberts EA, et al. NASPGHAN practice guidelines: diagnosis and management of hepatitis C infection in infants, children, and adolescents. *J Pediatr Gastroenterol Nutr*. 2012;54:838-855.
- Álvarez-Hernández G, Sotelo-Cruz N, Cano-Rangel A. Epidemiología del virus de la hepatitis C en niños. *Rev Mex Pediatr*. 2007;4:161-170.
- Wirth S. Current treatment options and response rates in children with chronic hepatitis C. *World J Gastroenterol*. 2012;18:99-104.
- Escobedo-Meléndez G, Fierro NA, Roman S, Maldonado-González M, Zepeda-Carrillo E, Panduro A. Prevalence of hepatitis A, B and C serological markers in children from western Mexico. *Ann Hepatol*. 2012;11:194-201.
- Broide E, Kimchi NA, Scapa E. Chronic hepatitis C infection in children. *Minerva Gastroenterol Dietol*. 2006;52:187-193.
- Narkewicz MR, Cabrera R, González-Peralta RP. The "C" of viral hepatitis in children. *Semin Liver Dis*. 2007;27:295-311.
- Yang CHT, Yoo ER, Ahmed A. The role of direct-acting antivirals in the treatment of children with chronic hepatitis C. *J Clin Transl Hepatol*. 2017;5:59-66.
- Viral Hepatitis Statistics and Surveillance. EE. UU.: Centers for Disease Control and Prevention; 2009.
- Tovo PA, Pembrey LJ, Newell ML. Persistence rate and progression of vertically acquired hepatitis C infection. *European paediatric hepatitis C virus infection*. *J Infect Dis*. 2000;181:419-424.
- Indolfi G, Resti M. Perinatal transmission of hepatitis C virus infection. *J Med Virol*. 2009;81:836-843.
- Spencer JD, Latt N, Beeby PJ, Collins E, Saunders JB, McCaughan GW, et al. Transmission of hepatitis C virus to infants of human immunodeficiency virus-negative intravenous drug-using mothers: rate of infection and assessment of risk factors for transmission. *J Viral Hepat*. 1997;4:395-409.
- Mast EE, Hwang LY, Seto DS, Nolte FS, Nainan OV, Wurtzel H, et al. Risk factors for perinatal transmission of hepatitis C virus (HCV) and the natural history of HCV infection acquired in infancy. *J Infect Dis*. 2005;192:1880-1889.
- Syriopoulou V, Nikolopoulou G, Daikos GL, Theodoridou M, Pavlopoulou I, Nicolaidou P, et al. Mother to child transmission of hepatitis C virus: rate of infection and risk factors. *Scand J Infect Dis*. 2005;37:350-353.
- Roberts EA, Yeung L. Maternal-infant transmission of hepatitis C virus infection. *Hepatology*. 2002;36:S106-S113.
- Resti M, Bortolotti F, Vajro P, Maggioro G. Guidelines for the screening and follow-up of infants born to anti-HCV positive mothers. *Dig Liver Dis*. 2003;35:453-457.
- Abdel-Hady M, Bunn SK, Sira J, Brown RM, Brundler MA, Davies P, et al. Chronic hepatitis C in children-review of natural history at a National Centre. *J Viral Hepat*. 2011;18:e535-e540.
- Rerksupphaphol S, Hardikar W, Dore GJ. Long-term outcome of vertically acquired and post-transfusion hepatitis C infection in children. *J Gastroenterol Hepatol*. 2004;19:1357-1362.
- Guido M, Rugge M, Jara P, Hierro L, Giacchino R, Larrauri J, et al. Chronic hepatitis C in children: the pathological and clinical spectrum. *Gastroenterology*. 1998;115:1525-1529.
- El-Shabrawi MH, Mohsen NA, Sherif MM, El-Karaksy HM, Abou-Yosef H, El-Sayed et al. Noninvasive assessment of hepatic fibrosis and necroinflammatory activity in Egyptian children with chronic hepatitis C virus infection using FibroTest and ActiTest. *Eur J Gastroenterol Hepatol*. 2010;22:946-951.
- Flores-Calderón J, Morán-Villota S, Ramón-García G, González-Romano B, Bojórquez-Ramos MC, Cerdán-Silva L, et al. Non-invasive markers of liver fibrosis in chronic liver disease in a group of Mexican children. A multicenter study. *Ann Hepatol*. 2012;11:364-368.
- Alkhouli N, Sedki E, Alisi A, Lopez R, Pinzani M, Feldstein AE, et al. Combined paediatric NAFLD fibrosis index and transient elastography to predict clinically significant fibrosis in children with fatty liver disease. *Liver Int*. 2013;33:79-85.
- Behairy Bel-S, Sira MM, Zalata KR, Salama el-SE, Abd-Allah MA. Transient elastography compared to liver biopsy and morphometry for predicting fibrosis in pediatric chronic liver disease: Does etiology matter? *World J Gastroenterol*. 2016;22:4238-4249.
- Lewindon PJ, Balouch F, Pereira TN, Puertolas-Lopez MV, Noble C, Wixey JA, et al. Transient liver elastography in unsedated control children: Impact of age and intercurrent illness. *J Paediatr Child Health*. 2016;52:637-642.
- Engelmann G, Gebhardt C, Wenning D, Wühl E, Hoffmann GF, Selmi B, et al. Feasibility study and control values of transient elastography in healthy children. *Eur J Pediatr*. 2012;171:353-360.
- Franchi-Abella S, Corno L, Gonzales E, Antoni G, Fabre M, Ducot B, et al. Feasibility and diagnostic accuracy of supersonic shear-wave elastography for the assessment of liver stiffness and liver fibrosis in children: a pilot study of 96 patients. *Radiology*. 2016;278:554-562.
- Dhyani M, Gee MS, Misraji J, Israel EJ, Shah U, Samir AE. Feasibility study for assessing liver fibrosis in paediatric and adolescent patients using real-time shear wave elastography. *J Med Imaging Radiat Oncol*. 2015;59:687-694.
- De-Lédinghen V, Le-Bail B, Rebouissoux L, Fournier C, Foucher J, Miette V, et al. Liver stiffness measurement in children using FibroScan: feasibility study and comparison with Fibrotest, aspartate transaminase to platelets ratio index, and liver biopsy. *J Pediatr Gastroenterol Nutr*. 2007;45:443-450.
- Breton E, Bridoux-Henno L, Guyader D, Daniélou H, Jouan H, Beuchée A, et al. Value of transient elastography in noninvasive assessment in children's hepatic fibrosis. *Arch Pediatr*. 2009;16:1005-1010.
- Yang LY, Fu J, Peng XF, Pang SY, Gao KK, Chen ZR, et al. Validation of aspartate aminotransferase to platelet ratio for diagnosis of liver fibrosis and prediction of postoperative prognosis in infants with biliary atresia. *World J Gastroenterol*. 2015;21:5893-5900.
- Shen QL, Chen YJ, Wang ZM, Zhang TC, Pang WB, Shu J, et al. Assessment of liver fibrosis by Fibroscan as compared to liver biopsy in biliary atresia. *World J Gastroenterol*. 2015;21:6931-6936.
- Hukkinen M, Kivisaari R, Lohi J, Heikkilä P, Mutanen A, Merras-Salmio L, et al. Transient elastography and aspartate aminotransferase to platelet ratio predict liver injury in paediatric intestinal failure. *Liver Int*. 2016;36:361-369.
- Leung DH, Khan M, Minard CG, Guffey D, Ramm LE, Clouston AD, et al. Aspartate aminotransferase to platelet ratio and fibrosis-4 as biomarkers in biopsy-validated pediatric cystic fibrosis liver disease. *Hepatology*. 2015;62:1576-1583.
- Pinto J, Matos H, Nobre S, Cipriano MA, Marques M, Pereira JM, et al. Comparison of acoustic radiation force impulse/serum noninvasive markers for fibrosis prediction in liver transplant. *J Pediatr Gastroenterol Nutr*. 2014;58:382-386.
- McGoogan KE, Smith PB, Choi SS, Berman W, Jhaveri R. Performance of the AST-to-platelet ratio index as a noninvasive marker of fibrosis in pediatric patients with chronic viral hepatitis. *J Pediatr Gastroenterol Nutr*. 2010;50:344-346.
- Pokorska-Spiwak M, Kowalik-Mikołajewska B, Aniszewska M, Pluta M, Marczyńska M. Is liver biopsy still needed in children with chronic viral hepatitis? *World J Gastroenterol*. 2015;21:12141-12149.
- Shneider BL, González-Peralta R, Roberts EA. Controversies in the management of pediatric liver disease: hepatitis B, C and NAFLD: summary of a single topic conference. *Hepatology*. 2006;44:1344-1354.
- Nydegger A, Srivastava A, Wake M, Smith AL, Hardikar W. Health-related quality of life in children with hepatitis C acquired in the first year of life. *J Gastroenterol Hepatol*. 2008;23:226-230.
- Rodríguez JR, Balistreri W, Haber B, Jonas MM, Mohan P, Molleston JP, et al. Impact of hepatitis C virus infection on children and their caregivers: quality of life, cognitive, and emotional outcomes. *J Pediatr Gastroenterol Nutr*. 2009;48:341-347.
- Garazzino S, Calitri C, Versace A, Alfaro A, Solfaro C, Bertina C, et al. Natural history of vertically acquired HCV infection and associated autoimmune phenomena. *Eur J Pediatr*. 2014;173:1025-1031.

45. Omland LH, Krarup H, Jepsen P, Georgsen J, Harritshøj LH, Riisom K, et al. Mortality in patients with chronic and cleared hepatitis C viral infection: a nationwide cohort study. *J Hepatol*. 2010;53:36-42.
46. Rumbo C, Fawaz RL, Emre SH, Suchy FJ, Kerkar N, Morotti RA, et al. Hepatitis C in children: a quaternary referral center perspective. *J Pediatr Gastroenterol Nutr*. 2006;43:209-216.
47. Baker RD, Baker SS. Hepatitis C in children in times of change. *Curr Opin Pediatr*. 2015;27:624-628.
48. González-Peralta RP, Langham MR, Andres JM, Mohan P, Colombani PM, Alford MK, et al. Hepatocellular carcinoma in 2 young adolescents with chronic hepatitis C. *J Pediatr Gastroenterol Nutr*. 2009;48:630-635.
49. Strickland DK, Jenkins JJ, Hudson MM. Hepatitis C infection and hepatocellular carcinoma after treatment of childhood cancer. *J Pediatr Hematol Oncol*. 2001;23:527-529.
50. Kelly D, Sharif K, Brown RM, Morland B. Hepatocellular carcinoma in children. *Clin Liver Dis*. 2015;19:433-447.
51. Bhatia V, Seth S, Kapoor A, Sibal A. Incidentally detected hepatocellular carcinoma in cirrhotic children. *Indian J Pediatr*. 2014;81:826.
52. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology*. 2009;49:1335-1374.
53. Wirth S, Pieper-Boustani H, Lang T, Ballauff A, Kullmer U, Gerner P, et al. Peginterferon alfa-2b plus ribavirin treatment in children and adolescents with chronic hepatitis C. *Hepatology*. 2005;41:1013-1018.
54. Feld JJ, Hoofnagle JH. Mechanism of action of interferon and ribavirin in treatment of hepatitis C. *Nature*. 2005;436:967-972.
55. Zeuzem S, Feinman SV, Rasenack J, Heathcote EJ, Lai MY, Gane E, et al. Peginterferon alfa-2a in patients with chronic hepatitis C. *N Engl J Med*. 2000;343:1666-1672.
56. Serranti D, Indolfi G, Resti M. New treatments for chronic hepatitis C: an overview for paediatricians. *World J Gastroenterol*. 2014;20:15965-15974.
57. Sung H, Chang M, Saab S. Management of hepatitis C antiviral therapy adverse effects. *Curr Hepat Rep*. 2011;10:33-40.
58. Narkewicz MR, Rosenthal P, Schwarz KB, Drack A, Margolis T, Repka MX, et al. Ophthalmologic complications in children with chronic hepatitis C treated with pegylated interferon. *J Pediatr Gastroenterol Nutr*. 2010;51:183-186.
59. Druyts E, Thorlund K, Wu P, Kanters S, Yaya S, Cooper CL, et al. Efficacy and safety of pegylated interferon alfa-2a or alfa-2b plus ribavirin for the treatment of chronic hepatitis C in children and adolescents: a systematic review and meta-analysis. *Clin Infect Dis*. 2013;56:961-967.
60. Jonas MM, Schwarz KB, Gonzalez-Peralta R, Lobritto S, Molleston JP, Murray KF, et al. Long-term growth outcomes in children treated for chronic hepatitis C. *J Pediatr*. 2014;165:1252-1254.
61. Granot E, Sokal EM. Hepatitis C virus in children: deferring treatment in expectation of direct-acting antiviral agents. *Isr Med Assoc J*. 2015;17:707-711.
62. Jonas MM, Balistreri W, González-Peralta RP, Haber B, Lobritto S, Mohan P, et al. Pegylated interferon for chronic hepatitis C in children affects growth and body composition: results from the pediatric study of hepatitis C (PEDS-C) trial. *Hepatology*. 2012;56:523-531.
63. Schwarz KB1, Gonzalez-Peralta RP, Murray KF, Molleston JP, Haber BA, Jonas MM, et al. The combination of ribavirin and peginterferon is superior to peginterferon and placebo for children and adolescents with chronic hepatitis C. *Gastroenterology*. 2011;140:450-458.
64. Sokal EM, Bourgeois A, Stéphenne X, Silveira T, Porta G, Gardovska D, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection in children and adolescents. *J Hepatol*. 2010;52:827-831.
65. Wirth S, Ribes-Koninckx C, Calzado MA, Bortolotti F, Zancan L, Jara P, et al. High sustained virologic response rates in children with chronic hepatitis C receiving peginterferon alfa-2b plus ribavirin. *J Hepatol*. 2010;52:501-507.
66. El-Karaksy HM, Mogahed EA, El-Raziky MS, Saleh D, Besheer M, Mubarak S. Safety and efficacy of combined treatment with pegylated interferon alpha-2b and ribavirin for HCV Genotype 4 in children. *J Interferon Cytokine Res*. 2016;36:1-8.
67. Bortolotti F, Indolfi G, Zancan L, Giacchinod R, Verucchie G, Cammà C, et al. Management of chronic hepatitis C in childhood: the impact of therapy in the clinical practice during the first 2 decades. *Dig Liver Dis*. 2011;43:325-329.
68. Rosen I, Kori M, Eshach-Adiv O, Yerushalmi B, Zion N, Shaoul R. Pegylated interferon alfa and ribavirin for children with chronic hepatitis C. *World J Gastroenterol*. 2013;19:1098-1103.
69. Pawłowska M, Pilarczyk M, Halota W. Virologic response to treatment with pegylated interferon alfa-2b and ribavirin for chronic hepatitis C in children. *Med Sci Monit*. 2010;16:CR616-CR621.
70. Al Ali J, Owayed S, Al-Qabandi W, Husain K, Hasan F. Pegylated interferon α -2b plus ribavirin for the treatment of chronic hepatitis C genotype 4 in adolescents. *Ann Hepatol*. 2010;9:156-160.
71. Wisniewska-Ligier M, Pawłowska M, Pilarczyk M, Halota W, Wozniakowska-Gesicka T. Efficacy of pegylated interferonalpha α -2b and ribavirin in chronic hepatitis C virus (genotypes 1 and 4) infection. *J Pediatr Gastroenterol Nutr*. 2013;57:694-699.
72. Suzuki M, Tajiri H, Tanaka Y, Takano T, Miyoshi Y, Murakami J, et al. Peginterferon therapy in children with chronic hepatitis C: a nationwide, multicenter study in Japan, 2004-2013. *J Pediatr Gastroenterol Nutr*. 2016;63:88-93.
73. Zhong YW, Zhang HF, Shi YM, Li YL, Chu F, Xu ZQ, et al. IL28B SNP rs12979860 is the critical predictor for sustained viral response in Chinese children aged 1 to 6 years with chronic hepatitis C. *Int J Biol Sci*. 2016;12:1357-1362.
74. Balistreri WF, Murray KF, Rosenthal P, Bansal S, Chuan-Hao L, Kersey K, et al. The safety and effectiveness of ledipasvir-sofosbuvir in adolescents 12 to 17 years old with hepatitis C virus genotype 1 infection. *Hepatology*. 2016;66:371-378.
75. Wirth S, Rosenthal P, González-Peralta RP, Jonas MM, Lin CH, Shao J, et al. Sofosbuvir and ribavirin in adolescents 12 to 17 years old with hepatitis C virus genotype 2 or 3 infection. *Hepatology*. 2017;66:1102-1110.
76. Fischler B, Priftakis P, Sundin M. Sofosbuvir and simeprevir treatment of a stem cell transplanted teenager with chronic hepatitis C infection. *Pediatr Infect Dis J*. 2016;35:708-710.
77. Thomas P, Santiago T, Dallas MH. Treatment of hepatitis C in a pediatric patient using simeprevir and sofosbuvir immediately after an umbilical cord blood transplantation. *Bone Marrow Transplant*. 2016;51:735-737.
78. Smith SK, Rosenthal P. Clearance of hepatitis C virus after fixed-dose combination ledipasvir/sofosbuvir in an adolescent female with decompensated cirrhosis. *J Pediatr Gastroenterol Nutr*. 2016;63:516-517.
79. Indolfi G, D'Antiga L. Treatment of hepatitis C virus infection in children: time for action. *Liver Transpl*. 2017;23:427-429.
80. Wirth S, Rosenthal P, Gonzalez-Peralta RP, Jonas MM, Balistreri WF, Lin CH, et al. Sofosbuvir and ribavirin in adolescents 12-17 years old with hepatitis C virus genotype 2 or 3 infection. *Hepatology*. 2017;66:1102-1110.
81. Indolfi G, Hierro L, Dezsofi A, Jahnel J, Debray D, Hadzic N, et al. Treatment of chronic hepatitis C virus infection in children: a position paper by the Hepatology Committee of European Society of Paediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr*. 2018;66:505-515.
82. A study to evaluate of hepatitis C virus infection in pediatric subjects (ZIRCON). EE. UU.: AbbVie; 2018.
83. Abdel-Ghaffar TY. Treatment of Egyptian hepatitis C genotype 4 infected children (and adolescents) with combined sofosbuvir & daclatasvir. EE. UU.: Yassin Abdelghaffar Charity Center for Liver Disease and Research/Egyptian Cure Bank/Society of Friends of Liver Patients in the Arab World; 2018.
84. Safety and efficacy of ledipasvir/sofosbuvir fixed dose combination +/- ribavirin in adolescents and children with chronic HCV-infection. EE. UU.: Gilead Sciences; 2018.
85. Sofosbuvir/velpatasvir in adolescents and children with chronic HCV infection. EE. UU.: Gilead Sciences; 2018.
86. Elbasvir (EBR)/grazoprevir (GZR) in pediatric participants with chronic hepatitis C infection (MK-5172-079). EE. UU.: Merck Sharp & Dohme Corp.; 2018.
87. Efficacy and safety of ledipasvir/sofosbuvir fixed dose combination in the treatment of hepatitis C virus (HCV) infection in pediatric participants undergoing cancer chemotherapy (Egypt Peds). EE. UU.: Gilead Sciences; 2018.
88. A study to evaluate the pharmacokinetics, safety, and efficacy of glecaprevir/pibrentasvir in pediatric subjects with genotypes 1-6 chronic hepatitis C virus (HCV) infection (DORA). EE. UU.: AbbVie; 2018.
89. Evaluation of daclatasvir (DCV) in combination with sofosbuvir (SOF) in children with chronic hepatitis C (CHC) infection. EE. UU.: Bristol-Myers Squibb; 2018.