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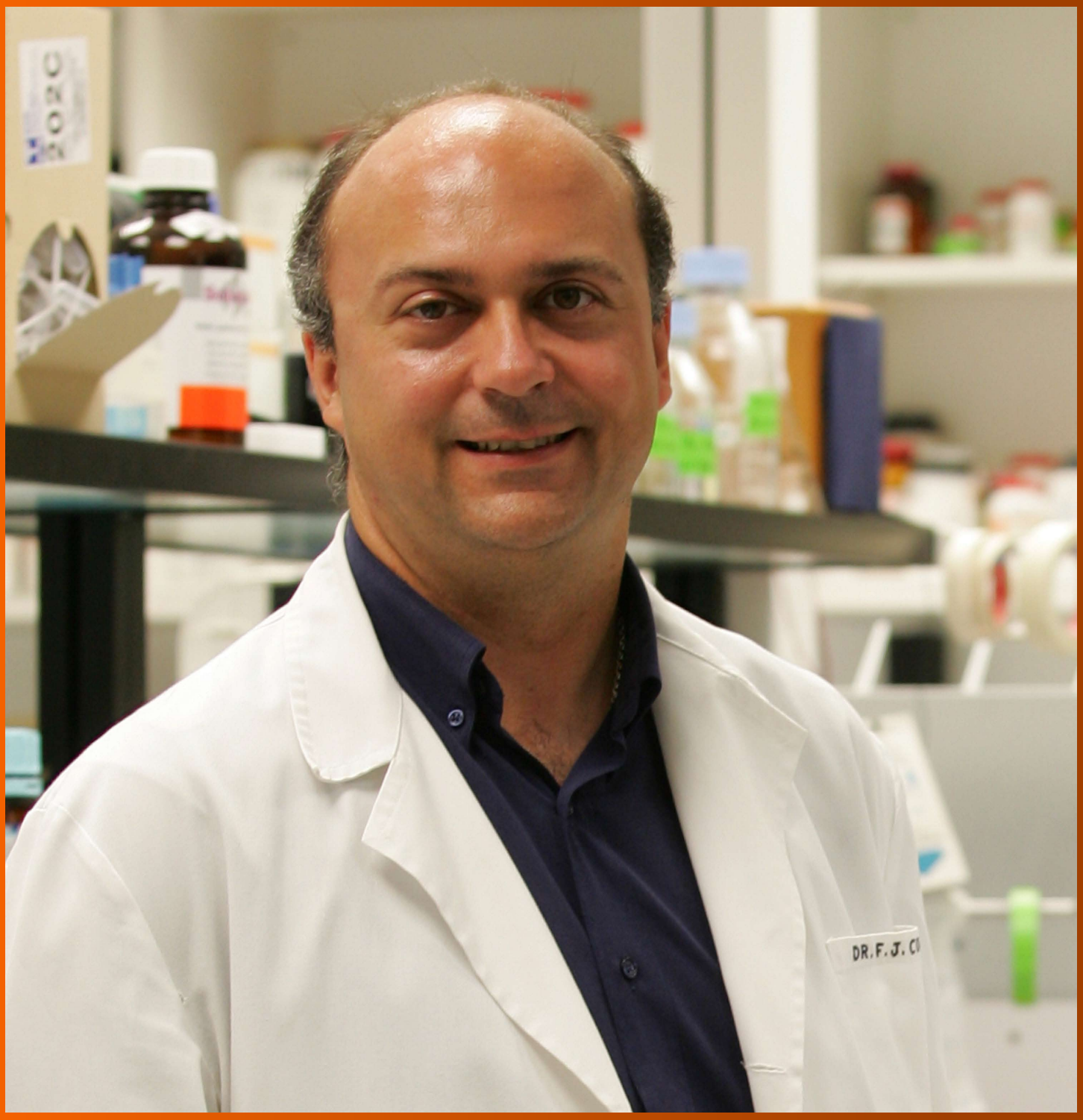

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AIMS AND SCOPE

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The primary task of *WJG* is to rapidly publish high-quality original articles, reviews, and commentaries in the fields of gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, hepatobiliary surgery, gastrointestinal oncology, gastrointestinal radiation oncology, gastrointestinal imaging, gastrointestinal interventional therapy, gastrointestinal infectious diseases, gastrointestinal pharmacology, gastrointestinal pathophysiology, gastrointestinal pathology, evidence-based medicine in gastroenterology, pancreatology, gastrointestinal laboratory medicine, gastrointestinal molecular biology, gastrointestinal immunology, gastrointestinal microbiology, gastrointestinal genetics, gastrointestinal translational medicine, gastrointestinal diagnostics, and gastrointestinal therapeutics. *WJG* is dedicated to become an influential and prestigious journal in gastroenterology and hepatology, to promote the development of above disciplines, and to improve the diagnostic and therapeutic skill and expertise of clinicians.

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REVIEW

Hepatitis C virus infection in children in the era of direct-acting antiviral

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Abstract

Hepatitis C virus (HCV) infection remains an important global health problem with chronic infection affecting approximately 11 million children worldwide. The emergence of direct-acting antiviral (DAA) therapies and the development of non-invasive methods for the determination of liver fibrosis will significantly improve the management of paediatric patients with chronic HCV infection in subsequent years. For paediatric patients, a new era of highly effective DAA agents is beginning, and the first results of available clinical trials are very promising. In this era, the identification and monitoring of patients continues to be an important issue. The availability of non-invasive serological and imaging methods to measure hepatic fibrosis enables the identification of patients with significant or advanced liver fibrosis stages. This article summarizes the current data on the epidemiology and progress of research aimed to evaluate the new therapies and non-invasive methods for liver injury in paediatric patients with chronic hepatitis C.

Key words: Biomarkers of liver injury; Adolescents; Epidemiology; Direct-acting antiviral; Hepatitis C virus; Non-invasive methods; Children

Core tip: There are more than 11 million hepatitis C virus (HCV)-infected children worldwide. Most new HCV-infected cases have occurred through vertical transmission. Currently, a new era of highly effective direct-acting antiviral agents for the treatment of HCV infection has begun for paediatric patients. The first results of clinical trials with interferon-free therapy are very promising. ESPGHAN developed a position paper for the

management of chronic HCV infection in children. Non-invasive methods to measure hepatic fibrosis enable the identification of patients with significant liver fibrosis. This article summarizes the current data on epidemiology, new therapies and non-invasive methods in paediatric patients with HCV infection.

Pawlowska M, Sobolewska-Pilarczyk M, Domagalski K. Hepatitis C virus infection in children in the era of direct-acting antiviral. *World J Gastroenterol* 2018; 24(24): 2555-2566 Available from: URL: http://www.wjgnet.com/1007-9327/full/v24/i24/2555.htm DOI: http://dx.doi.org/10.3748/wjg.v24.i24.2555

INTRODUCTION

Hepatitis C virus (HCV) infection is an important public health problem recognized by the WHO. The natural history of HCV infections in children is characterized by a long asymptomatic course, with low biochemical and histopathological activity[1,2]. The clinical symptoms of chronic HCV infection in children are not very characteristic (hepatomegaly, abdominal pain, nausea, vomiting, loss of appetite, joint pain); consequently, most HCV infections are diagnosed by chance. The inability to prevent infection by vaccination, together with the serious clinical consequences of liver cirrhosis, hepatocellular carcinoma and end-stage liver disease, are serious public health problems.

It is estimated that worldwide, 115-185 million people (2.8%) have a chronic HCV infection[3-6]. In the paediatric population alone, there are more than 11 million HCV-infected patients under 15 years of age, and more than 6 million of these children are viremic[7,8]. Higher frequencies of HCV infections are recorded in countries with low and medium incomes (1.8%-5%), and lower incidences are reported in countries with high incomes (0.05%-0.36%)[9].

The prevalence of hepatitis C antibodies in adults in North America is estimated at 1% to 1.5%[10], whereas it is estimated at 0.8% to 1.2% in Japan[11], 1.1% in Ghana[12], 1.0% in Malawi, 1.1% in Mozambique and 2.1% in Tanzania[13].

In a multi-centre study, the presence of anti-HCV antibodies in the central and eastern European population was reported as 0.27%-3.5%. The lowest values were recorded in Kosovo, Germany, the Czech Republic and Hungary (0.3%-0.6%), and the highest incidence of anti-HCV antibodies was found in Lithuania, Latvia and Romania (2.4%-3.5%). A study in Germany estimated the prevalence of anti-HCV antibodies to be 0.3%, and positive HCV viremia was estimated at 0.2%[14].

A study in Poland estimated the prevalence of anti-HCV antibodies at 0.91%, and positive HCV viremia was estimated at 0.6%, out of 278998 and 191405 patients from randomly chosen orthopaedic and trauma wards, respectively, together with health care workers and patients with diseases other than viral hepatitis[14]. In 2014, the world's highest incidence of anti-HCV antibodies was recorded in Egypt at 14.7%[15].

Geographic diversity of HCV genotypes has been observed. Genotype 1 (46.2% of HCV infections) is the most widespread worldwide and is responsible for most infections in developed countries. The second most frequent is genotype 3 (30.1% of HCV infections), which is often found in South Asia and in Europe and the US among drug users infected with HCV. Genotype 2 (9.1% of HCV infections) and genotype 6 (5.4%) are the most common genotypes found in East Asia. Genotype 4 is prevalent in North Africa and the Middle East (8.3% of HCV infections). Genotype 5 accounts for less than 1% of HCV infections and mainly appears in Africa, whereas genotype 7 infection was confirmed in Canada in 1 patient of central African origin[16-18].

The prevalence of anti-HCV antibodies in children varies geographically, as in the adult population. Before 1992, children treated with blood or blood products were amongst the high-risk groups for HCV infection. Before 1992, HCV-infected children acquired the virus through the transfusion of blood and blood-related products. Since 1992, transfused blood units have mostly been free of HCV, which is estimated to be present at a frequency of 0.001% to 0.01% per transfusion[19]. Therefore, most new HCV-infected cases have occurred through vertical transmission[8]. It is estimated that maternal-foetal transmission is responsible for more than 60% of children with HCV, and approximately 5% of infants are born to HCV-RNA-positive mothers[20]. The risk is higher in HCV-positive women with a high viremia in their pregnancy and HIV co-infection[21,22].

In the USA, an estimated 23000 to 46000 children live with chronic HCV. The positive presence of anti-HCV antibodies has been confirmed in 0.17% of children aged 6 to 11 and in 0.39% of those aged 12 to 19, with the most common being genotype 1, followed by genotypes 2 and 3, and more rarely genotypes 4 and 6[1,8,10]. In Japan, the prevalence of HCV infection in children is estimated at 0.012% in those aged 5-9 years, 0.010% at 10-14 years, and 0.022% at 15-19 years, with genotype 2 being the most prevalent in these children. Research by Mizuochi *et al*[23] confirmed that vertical transmission has increased and accounts for over 99% of all new HCV cases in the last decade. No transfusion-related cases have been observed since 1994[23,24]. In Turkey, the prevalence of HCV infection in children and adults is estimated to be 0-1%, and in Syria, 1%-2%[25,26]. In India, the prevalence of HCV infection in children is estimated at 3.6% in those aged 1-9 years, and in Egypt, the prevalence is estimated at 2.02% in ages 1-9 years[27,28]. According to Lagging *et al*[29], the prevalence of chronic HCV infection is less than 0.5% among European children. During the past decade, approximately 100 such cases have been reported annually to the Swedish Public Health Agency, with half occurring in those younger than 16 years of age[30]. In light of the expected annual number of

Table 1 Ongoing clinical trials to evaluate the safety and efficacy of direct-acting antivirals in children with chronic hepatitis C

Trial identifier	Drug tested	HCV genotype
NCT 3067129	Glecaprevir/pibrentasvir	1-6
NCT 2486406	Ombitasvir/paritaprevir/ritonavir ± dasabuvir ± ribavirin	1,4
NCT 3080415	Sofosbuvir + daclatasvir	4
NCT 2868242	Ledipasvir/sofosbuvir	1,4
NCT 2249182	Ledipasvir/sofosbuvir ± ribavirin	1,4,5,6
NCT 3022981	Sofosbuvir/velpatasvir	1-6
NCT 2985281	Gratisovir + ribavirin	1-6

HCV: Hepatitis C virus.

infections secondary to mother-child transmission[31] and the number of children immigrating to Sweden from countries with a higher HCV prevalence, this number may be an underestimation of the true incidence[29].

In Poland, the prevalence of HCV infection in children in the study by Gołębiowska and colleagues was estimated at 2.8%[32].

The largest group of HCV-infected children is comprised of children infected via maternal-foetal transmission. Other groups include children with HIV infection, children with a history of multiple sexual partners, adolescents with a history of intravenous drug use and children who are victims of sexual assault. The prevalence of substance use amongst children with HCV increased from 25% in 2006 to 41% in 2012[33]. Screening for hepatitis C should be considered for those children with risk factors for HCV and for pregnant women.

DIRECT-ACTING ANTIVIRAL THERAPY

The development of oral interferon-free (IFN-free) anti-HCV treatment with direct-acting antivirals (DAAs) has revolutionized the therapy of HCV infection. Currently, highly effective, safe and well-tolerated antiviral regimens are available to treat adults with hepatitis C infection[34].

In 2017, the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) approved the use of the fixed-dose combination of ledipasvir/sofosbuvir and of the combination of sofosbuvir and ribavirin for the treatment of adolescents with chronic hepatitis C virus (HCV) genotypes 1, 4, 5 and 6 and genotype 2 and 3 infections, respectively. Trials with direct acting antivirals (DAAs) are ongoing for younger children. The drugs currently licensed in Europe and the US for the treatment of chronic HCV infection in children include IFN, PEG IFN, ribavirin and, recently, the fixed-dose combination of ledipasvir/sofosbuvir and sofosbuvir for the treatment of adolescents aged 12-17 years weighing more than 35 kg. The only drugs currently approved for children younger than 12 are PEG IFN α-2a or -2b and ribavirin. Children with HCV genotypes 1 or 4 infection should be treated for 48 wk whereas those infected with genotypes 2 or 3 should be treated for 24 wk[20,35-39]. Few data are available on the paediatric use of DAAs, and 7 clinical trials are currently ongoing (NCT 3067129, NCT 2486406, NCT 3080415, NCT 2868242, NCT 2249182, NCT 3022981, NCT 2985281[34,40]) (Table 1).

The first study assessing the IFN-free treatment of HCV-infected adolescents was a phase 2, multicentre, open-label study that included 100 patients aged 12-17 years who were infected with genotype 1 HCV who received a combination tablet of 90 mg ledipasvir and 400 mg sofosbuvir once daily for 12 wk[41]. Serial pharmacokinetic (PK) blood samples were assessed on day 10 of the study in the first 10 patients. These patients participated in a PK lead-in cohort to determine the pharmacokinetics of sofosbuvir, ledipasvir and the sofosbuvir metabolite GS-331007 to confirm the appropriateness of the adult dose of ledipasvir/sofosbuvir in adolescents before additional patients were enrolled. To be eligible for the PK lead-in cohort, the adolescents had to weigh > 45 kg, be naïve to HCV treatment and not have liver cirrhosis. They were administered ledipasvir/sofosbuvir with a standardized meal with more than 400 kcal and 13 g of fat.

In the entire analysed group of adolescents, 80% were HCV treatment-naive, 81% were infected with genotype 1a HCV, and 84% were infected through perinatal transmission. One patient had cirrhosis, and 42 did not; the degree of fibrosis was unknown in 57 patients. Of the 99 patients who completed treatment, 2 patients did not attend the follow-up visits at weeks 4 and 12. One of those patients completed the follow-up visit at 24 wk after the end of treatment. A sustained virologic response at 12 wk (SVR 12), defined as an HCV RNA level less than the lower limit of quantification (15 IU/mL), was achieved in 98% of patients. No patient had virologic failure. The presence of resistance-associated substitutions (RASs) at baseline did not affect the treatment response. All patients with a baseline presence of NS5A or NS5B RAS achieved SVR12. The most commonly reported adverse events were headache (27% of patients), diarrhoea (14%) and fatigue (13%). No serious adverse events or significant abnormalities in laboratory results were reported. Most laboratory abnormalities were mild; 1 patient had a grade 4 aspartate aminotransferase (AST) elevation up to 573 U/L at the week 4 follow-up visit. This event was associated with the initiation of isotretinoin treatment for acne, and the patient's AST levels decreased and normalized. The administration of ledipasvir/sofosbuvir did not affect development as assessed by Tanner pubertal staging.

Ledipasvir-sofosbuvir was highly effective at treating adolescents with chronic HCV genotype 1 infection. The dose of ledipasvir-sofosbuvir currently used in adults was well tolerated in adolescents and had an appropriate pharmacokinetic profile[41]. No data are currently available on possible shortening of the treatment to 8 wk as suggested in adults if their baseline HCV RNA level is less than 6 million (6.8 log) IU/mL[42].

Previous studies have demonstrated that both the physical and psychosocial health and cognitive functioning of asymptomatic children with chronic HCV infection are significantly reduced compared to children without HCV[43,44]. Chronic HCV infection has been associated with the impairment of health-related quality of life (HRQL) in both adult and paediatric patients. Nyddeger *et al*[43] assessed the HRQL of 19 HCV-infected Australian children using self-reports from the children and reports from their parents. The study revealed that physical and psychosocial summary scores were significantly lower than in children not infected with HCV. This impairment was particularly notable in the General Health and Parent impact-emotional scales; children with HCV also reported reduced physical functioning[43]. In a PEDS-C study that included 114 HCV-infected children, caregivers assessed their children as being in poor health pre-treatment, whereas the children and adolescents themselves reported scores equal to the normative population[45].

Younossi *et al*[46] were the first to assess HRQL in adolescents infected with genotype 1 HCV who were treated with ledipasvir/sofosbuvir. HRQL was assessed using the PedsQLv4.0-SF15 completed by the children and their caregivers before, during and after treatment. The PedsQLv4.0-SF15 includes 15 items that represent 4 domains of adolescent daily functioning (physical, emotional, social and school functioning). At baseline, the caregivers' and self-reported school functioning scores were significantly lower in adolescents with HCV infection ($P < 0.05$). All but 1 HRQL score was substantially lower when reported by caregivers compared to the adolescents' self-reports. A potential reason for the consistently lower perception of HRQL by caregivers than that reported by the adolescents themselves is that parents' perceptions may be biased by their own experience with HCV infection (84% of subjects acquired their infection prenatally). This notion is supported by the observations in the PEDS-C study showing that infected mothers who had transmitted HCV to their offspring had worse HRQL compared to uninfected caregivers. At the end of treatment, no treatment-related impairments in HRQL scores were reported by the subjects or their caregivers. Significant improvement in the adolescents' self-reported emotional function domain was noted in the post- treatment period. At the end of 24 wk of follow-up, all HRQL scores except for the school functioning scores became similar to the population norms without HCV[46]. This was the first clinical trial of an interferon- and ribavirin-free regimen in children with HCV infection that showed not only a very high efficacy and a favourable safety profile of LDV/SOF but also an improvement of HRQL scores after achieving SVR, which was sustained for months after treatment cessation[46].

The preliminary results of the fixed-dose combination of ledipasvir/sofosbuvir in children aged 6 to 11 years old was presented at the International Liver Congress in 2017[47]. This prospective, open-label, uncontrolled trial enrolled 90 patients, all of whom received ledipasvir (45 mg) and sofosbuvir (200 mg) once daily for 12 wk. Eighty-six (96%) of the patients were infected by HCV genotype 1, 18 (20%) were treatment-experienced and 2 had cirrhosis. In total, 99% (89/90) of the treated children achieved SVR12. One genotype 1a patient with cirrhosis relapsed at the fourth follow-up visit. The most commonly reported adverse events were headache (19%), fever (17%) and abdominal pain (15%).

In a recently published prospective, open-label, uncontrolled registration trial, 52 patients were treated with sofosbuvir (400 mg) once daily and weight-based ribavirin (15 mg/kg) twice daily for 12 (genotype 2) or 24 (genotype 3) wk[48]. The pharmacokinetics of sofosbuvir and its metabolite GS-331007 were evaluated by intensive plasma sampling on day 7 in the first 10 patients. Forty-three (83%) of the patients were treatment-naïve, 73% were infected by vertical transmission and 75% had genotype 3 HCV. None of the patients who underwent liver biopsy had cirrhosis. SVR12 was achieved in 98% (51/52) of cases. The SVR12 rates were 100% (13/13) for patients with genotype 2 and 97% (38/39) for genotype 3. The single patient who did not achieve SVR12 was lost to follow-up after achieving SVR4. The most commonly reported adverse events were nausea (27%) and headache (23%). Sofosbuvir and ribavirin were safe and highly effective in adolescents with chronic HCV genotype 2 or 3 infections[48]. To assess the HRQL of 50 HCV-positive adolescents treated with SOF + RBV, the patients and their parents completed the PedsQL-4.0-SF-15 questionnaire at baseline, at the end of treatment and during post-treatment follow-up[49]. During treatment with SOF + RBV, there were no significant decrements in any of the patients' self-reported or parent-reported scores, regardless of treatment duration. After treatment cessation, a statistically significant improvement in the patients' self-reported social functioning scores by post-treatment week 12 was recorded. A multivariate analysis showed that a history of abdominal pain and psychiatric disorders affected impaired HRQL in adolescents with HCV ($P < 0.05$). Adolescents with HCV did not appear to experience any reductions in HRQL during treatment with SOF + RBV and experienced some improvements in their HRQL scores after achieving SVR.

Hashmi *et al*[50] assessed the effectiveness and safety of the combined administration of sofosbuvir (400 mg) once daily and ribavirin (10-15 mg/kg/d) in treatment-naïve children with HCV infection aged 5 to 18 years. The total therapy duration was 24 wk. Thirty-five patients with a mean age of 10.24 ± 2.80 years, including 22 boys and 13 girls, were included. The most common

Table 2 Efficacy of direct-acting antivirals treatment of hepatitis C virus infected children and adolescents

Study	Patient population	HCV genotype	Drug	Duration of therapy (wk)	SVR 12 (%)
Balistreri *et al*[41]	100 adolescents aged 12-17 yr	1	ledipasvir 90 mg + sofosbuvir 400 mg	12	98
Murray *et al*[47]	90 children aged 6-11 yr	1	ledipasvir 45 mg + sofosbuvir 200 mg	12	98
Wirth *et al*[48]	13 adolescents aged 12-17 yr	2	sofosbuvir 400 mg + ribavirin 15 mg/kg	12	100
	39 adolescents aged 12-17 yr	3	sofosbuvir 400 mg + ribavirin 15 mg/kg	24	97
Hashmi *et al* [50]	35 children aged 5-18 yr	3,1	sofosbuvir 400 mg + ribavirin 10-15 mg/kg	24	97
Leung *et al* [52]	38 adolescents	1,4	ombitasvir 150 mg + paritaprevir 100 mg + ritonavir 25 mg ± dasabuvir 250 mg ± ribavirin	12-24	100
El-Sayed *et al* [53]	13/18 adolescents	4	sofosbuvir 400 mg + daclatasvir 60 mg ± ribavirin 15 mg/kg	8-12	100

HCV: Hepatitis C virus; SVR: Sustained virologic response.

HCV genotype was genotype 3, which was encountered in 27 (77.15%) children, followed by genotype 1 in 6 children (17.14%). Most of the patients had pre-existing haematological disorders including thalassemia major, acute lymphoblastic leukaemia, non-Hodgkin's lymphoma, von Vilebrand disease and Hodgkin's disease. The most frequent mode of HCV transmission was via blood products transfusion (42.86%), followed by perinatal transmission. Thirty (85.71%) patients achieved a rapid virological response with undetectable HCV RNA by 4 wk of treatment, whereas the remaining 5 (14.28%) children were HCV RNA negative by 12 wk of treatment. An end-of-treatment response was achieved for all patients, and SVR12 was achieved by 34 (97.14%) patients. The treatment was well tolerated[50].

Clinical trials of interferon-free DAA regimens have been initiated for children ages 3-17 years. There is hope that increased DAA uptake may prevent paediatric HCV infections by shrinking the pool of infectious persons. DAA therapies may also help reduce new vertically and horizontally acquired paediatric infections[51].

In the recently presented prospective, open-label, uncontrolled ZIRCON trial, 38 adolescents with HCV genotype 1 or 4 infections were enrolled and treated with ombitasvir/paritaprevir/ritonavir (150/100/25 mg once daily) with dasabuvir (only for those with genotype 1 infection; 250 mg twice daily) and/or ribavirin (for all patients with genotype 1a or 4 infection; 15 mg/kg divided twice daily)[52]. All patients received 12 wk of treatment, except for one patient with an HCV genotype 1a infection with cirrhosis who was treated for 24 wk. Twenty-five (66%) of the patients were treatment-naïve, and 37 (97%) were non-cirrhotic. All 38 patients achieved SVR12 (100%). The most commonly reported adverse events were headache (21%) and asthenia (18%)[52]. The preliminary data from a prospective, open-label, uncontrolled trial on combined therapy with sofosbuvir, daclatasvir with or without ribavirin (400 mg + 60 mg + 15 mg/kg) of 13 adolescents with HCV genotype 4 infection were presented. The SVR was 100%[53].

The results of the first clinical and observational trials with IFN-free therapy are very promising. The efficacy of DAAs treatment in HCV infected children was presented in Table 2.

RECOMMENDATIONS FOR THE TREATMENT OF CHRONIC HCV INFECTION IN CHILDREN

Although new treatments are expected to be approved for paediatric use for all age groups in the near future, there is uncertainty on the current optimal approach to treat children with chronic HCV infection[34,54]. The Hepatology Committee of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) developed an evidence-based position paper for the management of chronic HCV infection in children. This position paper addresses therapeutic management issues including goals, endpoints, indications, contra-indications and the optimal treatment regimen in children with chronic HCV infection. The present position paper advocates the treatment of adolescents with chronic HCV infection and is directed to health authorities to recognize the importance of treating this special group of patients affording the cost of treatment[40].

The goal of therapy in children is to cure HCV infection to prevent the possible progression of HCV-related liver disease and its complications (A1).

The endpoint of therapy in children is undetectable HCV RNA in the blood by a sensitive assay (lower limit of detection $\leqslant$ 15 IU/mL) 12 wk (SVR12) after the end of DAA treatment or 24 wk (SVR24) after the end of PEG IFN and ribavirin (A1).

The rationale underlying the indications for treatment of adults with chronic infection is also valid for children (B1).

All treatment-naïve and treatment-experienced children with chronic HCV infection are considered for therapy (A1).

Liver biopsy for obtaining liver tissue for histopathologic examination is not routinely indicated in children with chronic HCV infection but should be evaluated case-by-case (A1).

Treatment is considered without delay in the pres-

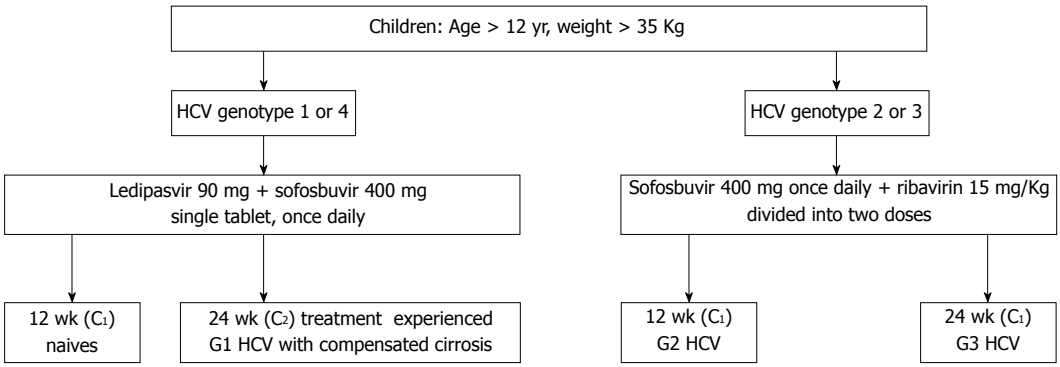

Figure 1 Recommended treatment of hepatitis C virus infected children. HCV: Hepatitis C virus.

ence of significant fibrosis and cirrhosis, extrahepatic manifestations and co-morbidities that increase the risk of rapid evolution of liver disease (solid organ or haematopoietic stem cell transplant recipients, other patients undergoing immunosuppressive treatments) (A1).

Treatment can generally be deferred in age-cohorts where combined PEG IFN and ribavirin is the only treatment option (C1).

IFN-free regimens are the best options in HCV-infected adolescents (> 12 years of age, weight > 35 kg), independent of the stage of liver disease and of co-morbidities (C1).

PEG IFN and ribavirin have not been recommended for the treatment of HCV-infected adolescents since 2017 (C1).

Treatment of HCV genotype 1 or 4 infection: Children older than 12 years who weigh > 35 kg and are chronically infected with HCV genotype 1 or 4 should be treated with the combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with a single tablet administered once daily for 12 wk (C1). The recommended duration of therapy for treatment-experienced children with HCV genotype 1 infection and with compensated cirrhosis is 24 wk (C2).

Treatment of HCV genotype 2 or 3 infection: (1) Children older than 12 years who weigh > 35 kg and are chronically infected with HCV genotype 2 should be treated with sofosbuvir (400 mg) once daily and weight-based ribavirin (15 mg/kg divided into 2 doses) for 12 wk (C1). And (2) Children older than 12 years who weigh > 35 kg and are chronically infected with HCV genotype 3 should be treated with sofosbuvir (400 mg) once daily and weight-based ribavirin (15 mg/kg divided into 2 doses) for 24 wk (C1) (Figure 1).

Treatment of chronic HCV infection in children younger than 12 years

PEG IFN and ribavirin are no longer recommended as a general treatment for children younger than 12 years who are infected with HCV (C1).

In children younger than 12 years, the decision to initiate therapy should be individualized to isolated cases based on the HCV genotype, severity of liver disease (as assessed by liver biopsy), potential for side effects, likelihood of response and presence of co-morbidities. These cases should be referred to a centre with experience in the treatment of children with chronic HCV infection, and the possible off-label use of DAAs could be considered (C1)[40].

The goal of therapy in children with chronic HCV infection is to cure the infection. The risk of HCV-related hepatic and extra-hepatic complications in children is significantly lower than that for adults. Long-term follow-up paediatric studies, with combined therapy with IFN or PEGIFN + ribavirin, have shown that SVR24 corresponds to a definitive cure of HCV infection in 98% to 100% of cases[55,56]. The availability of safe IFN-free regimens for adolescents older than 12 years and weighing > 35 kg makes these the best options in treatment-naïve and treatment-experienced patients, independent of the stage of liver disease and of the presence or absence of co-morbidities. Consequently, the combination of PEG IFN and ribavirin is no longer recommended.

NON-INVASIVE EVALUATION OF LIVER DISEASE SEVERITY

The clinical management of children with chronic hepatitis C (CHC) remains under discussion. Prognosis, risk stratification and treatment decision depend on histological severity determined by liver biopsy. CHC children belong to a low-risk group for progressive liver disease, which allows for the postponement of treatment in most children[57,58]. Notably, at the present time, more effective and better tolerated interferon-free therapies are not yet available for children in clinical practice in the wide range they are available for adult patients. Although the degree of liver damage generally depends on age and the duration of infection, the results of available paediatric studies suggest that treatment can be postponed until adolescence or adulthood, unless patients show rarely observed progression of liver disease[35]. With the development of interferon-free treatment regimens, it is reasonable to wait until adolescence or until DAAs are approved to routine clinical use for all age groups of children. Therefore, children require close follow-

up of their liver disease stage and grade to detect the appropriate time to begin antiviral treatment.

Currently, liver biopsy remains important for the evaluation of the fibrosis grade and necro-inflammatory activity in patients with CHC, particularly in patients with concomitant HBV and HIV infection, liver steatosis or autoimmune hepatitis. However, this method has its limitations, including very small needle biopsy specimens, which may be unrepresentative of the rest of the liver (sampling error) and difficult to omit different interpretations of the same sample by different pathologists (observer variability)[59]. In addition, liver biopsy is an invasive examination associated with possible severe complications; it is unpleasant for the patient and not suitable as a screening test or to monitor the effects of liver disease treatment. Potential complications, although rare, make the liver biopsy less accepted in paediatric patients than in adults[60]. Given these limitations, liver biopsy among CHC children is performed much less frequently than among adults and most often applies to cases with persistent liver dysfunction or with co-morbidities. Thus, almost two decades of research aimed at investigating and implementing non-invasive methods for the accurate evaluation of liver fibrosis has been important for the CHC paediatric population.

SERUM BIOMARKER TESTS

There is great interest connected to the possibility of identifying stages of liver fibrosis by using non-invasive markers based on blood tests[61]. The most extensively studied test was the FibroTest, a serological test that indirectly assesses the processes of fibrogenesis by measuring the serum levels of fibrosis biomarkers. The FibroTest consists of an algorithm that detects levels of the following 5 serum fibrosis markers: alpha-2-macroglobulin, haptoglobin, apolipoprotein-A1, bilirubin and gamma-glutamyl-transpeptidase, resulting in scores adjusted according to age and gender, which should correspond to the histopathological fibrosis scales. ActiTest, another non-invasive test that identifies necro-inflammatory activity, results in scores that should correspond to the histopathological activity scales. ActiTest uses an algorithm based on the FibroTest results and serum alanine aminotransferase (ALT) activity[62,63].

The FibroTest-ActiTest has been tested and validated in adults chronically infected with HCV[64]. FibroTest-ActiTest scores adjusted according to age suggest that results from adult studies should correspond to predicting advanced fibrosis in children. Currently, there are limited data on the usefulness of biomarkers in cohorts of CHC paediatric patients. The results of the few available studies that have compared serological markers with histopathological evaluations revealed that serological markers have limited clinical potential in children with CHC. In the Hermeziu *et al*[65] study, test results from the FibroTest-ActiTest were in line with histopathological METAVIR scores in 48% (10/21) of paediatric cases. Studies on children with chronic liver disease of different aetiologies showed that FibroTest scores and the APRI *(aspartate aminotransferase-to-platelet ratio index)* can differentiate between non-fibrosis and significant fibrosis and thus can be recommended only to detect patients with cirrhosis or significant fibrosis (METAVIR F3-F4)[66,67]. Another study, including 50 Egyptian children with CHC, revealed the utility of the FibroTest to discriminate between patients with mild (F1) and advanced fibrosis scores at F2-F4, and between patients with no fibrosis (F0) and with fibrosis (F1-F4)[68]. Compared to biopsy, the overall accuracy of the FibroTest for detecting fibrosis (F1-F4) and advanced fibrosis (F2-4) was 94% and 88%, respectively. Researchers have shown the discrimination ability of the ActiTest between patients with mild and moderate activity with an overall accuracy of 90%. Additionally, studies demonstrated a highly significant linear correlation between the FibroTest-ActiTest results and the fibrosis stages and inflammation activity grades. Conversely, the Pokorska-Śpiewak *et al*[69] study revealed that the FibroTest-ActiTest was poorly correlated with the histopathological evaluation in paediatric patients with chronic viral hepatitis. We are constantly searching for new, more specific markers of liver fibrosis. A single study conducted in CHC children tested the significance of markers such as the C4a Complement[70] and inter-alpha-trypsin inhibitor heavy chain 4 (ITIH4)[71], which was not associated with liver fibrosis scores but could predict significant fibrosis. The results of a recent study indicated that the non-invasive biomarkers APRI, FIB-4 and AST modified by the body mass index z-score have a good to excellent performance for detecting significant liver fibrosis[72]. In addition, the authors found that these biomarkers, adjusted by the BMI z-score, perform excellently for diagnosing significant steatosis in children with CHC.

According to these data, although serological markers do not correlate adequately with the histopathological evaluation in children, they can still be useful for selecting patients with advanced-stage liver injury who should undergo liver biopsy. In fact, the assessment of the usefulness of these tests in adults indicates that they are reliable in distinguishing extreme stages of histopathological fibrosis; however, they are less effective in determining intermediate degrees of fibrosis[63]. Therefore, in children with the most prevalent intermediate stages of hepatic fibrosis progression, these tests will have limited clinical utility. Conversely, even if these tests are not as accurate as a liver biopsy, their ability to exclude liver cirrhosis becomes more important as a screening tool in all paediatric patients with chronic hepatitis C, which would allow many patients to avoid biopsy.

PHYSICAL TECHNIQUES

The rise in popularity of minimally invasive diagnoses has led to advances in radiographic techniques of imaging modalities for diagnosing hepatic fibrosis. During the past decade, new imaging techniques have become

increasingly accepted for diagnosing the severity of liver disease. New radiologic imaging methods estimate liver fibrosis by assessing the tissue elasticity, which increases along with the increasing stages of fibrosis. These techniques include several types of an ultrasound-based elastography such as transient elastography (TE), shear wave elastography (SWE), acoustic radiation force impulse imaging (ARFI), supersonic shear-wave elastography (SSWE) and magnetic resonance elastography (MRE), which is based on magnetic resonance imaging (MRI)[62,73,74]. All these techniques estimate tissue stiffness by measuring the velocity of the sound waves passing through the liver (shear wave velocity). The value of the shear wave (in m/s) is then converted into kilopascals to indicate liver stiffness. A higher kPa reflects a stiffer liver and more severe liver fibrosis.

Among these new techniques, TE is the most commonly used[75,76]. The main technical limitation of Fibroscan is the inability to preview the precise location of the measurements; furthermore, there is no possibility to measure patients who have ascites or individuals who are morbidly obese[77]. The accuracy of TE has been shown to be excellent in several studies of adults with chronic hepatitis C[74,78-81]. Overall, the published studies on children and adolescents that have compared different non-invasive tools for liver stiffness measurement (LSM) with liver biopsies are limited. Well-designed relatively large paediatric studies using LSM to predict fibrosis stages are scarce. The only paediatric study evaluating the utility of TE (FibroScan) in liver fibrosis using the METAVIER score in a cohort of 30 chronic hepatitis C patients is from Egypt by Awad *et al*[82]. They found that the highest predictive performance of TE was detected for liver cirrhosis, followed by advanced fibrosis (F3). The accuracy for the discrimination of liver cirrhosis and advanced fibrosis was 96.7% and 85.3% at cut-off values of 9.5 and 12.5 kPa, respectively.

Because of the lack of available studies on children with CHC, our knowledge of the usefulness of these techniques is currently primarily based on the results of research conducted on children with chronic liver disease (CLD), including nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), Wilson disease, autoimmune hepatitis or liver transplantation recipients, and finally patients with chronic viral hepatitis[66,83-93]. In 2 available studies amongst children with miscellaneous paediatric CLD including subgroups of patients with CHC, the TE (FibroScan) results were compared to liver biopsy. They provided evidence that FibroScan results were correlated with the fibrosis stages and can be reliable for distinguishing severe stages of liver fibrosis[66,88]. Other studies in paediatric CLD patients demonstrate that ultrasound-based elastography is a reproducible and accurate tool for identifying patients without any degree of fibrosis or significant fibrosis ($F \geqslant 2$), with advanced fibrosis ($F \geqslant 3$) and with cirrhosis (F4), with a detection rate > 90%. This method was less accurate in discriminating between early stages of fibrosis (F0-F2). The authors observed that the stiffness values overlap considerably between early degrees of liver fibrosis. Although paediatric study results suggest that the fibrosis cut-off values are similar to those in adults, a small heterogeneous population does not allow for setting specific cut-off values for children[94-96]. Moreover, the diagnostic high accuracy demonstrated by the authors may be overestimated because of the heterogeneity of the studies, the small sample size, the small number of children with significant or severe fibrosis and problems with interpretations of liver biopsies in children caused by the diversity of the disease. As in adults, the increased necroinflammatory grade can increase liver stiffness values and therefore can confound the prediction of liver fibrosis using ultrasound elastography[82,84,97]. The results of a prospective cross-sectional study including a total of 90 children with 3 different aetiologies of chronic liver disease (CHC, AIH and Wilson disease) were recently shown[88]. In this study, higher elastography values for different stages in AIH patients compared to the other studied groups were observed, which - according to the authors - was connected to higher grades of inflammatory activity in AIH. However, AIH is a particularly prominent disease in this respect. Another study amongst CLD children showed that the presence of steatosis significantly increased the SWE values[85]. Therefore, this technique should still undergo evaluation for specific liver conditions.

MR elastography is an alternative method for determining liver fibrosis. The main advantage of EMR is its very high accuracy of measuring liver stiffness, due to the opportunity to investigate a larger volume of liver tissue. MRE can discriminate patients with moderate and severe fibrosis from those with mild fibrosis with a high sensitivity and specificity[98]. High research costs indicate that it has limited applications in clinical practice. Currently, there are no test results using MRE to analyse liver fibrosis in a cohort of patients with CHC. Two available studies on children and adolescents with CLD who are undergoing MRE and liver biopsy showed excellent accuracy of MRE for detecting significant fibrosis[99,100]. Moreover, by using MR elastography, Trout *et al*[99] confirmed the importance of a confounding effect of steatosis or inflammation of liver stiffness values on the example of a subgroup of patients with NFLD.

Paediatric studies have revealed that the improved diagnostic accuracy of liver fibrosis can be reached using a combination of non-invasive methods[83,97]. Therefore, more and more studies in children concern the clinical utility of combining 2 or more non-invasive fibrosis tests in children, and the first studies aimed at comparing the diagnostic performance of 2 imaging methods in a group of children to evaluate its correlation and utility in assessing liver fibrosis have been conducted[101].

CONCLUSION

The largest group of children infected with HCV consists of children born with maternal-foetal HCV transmission. Other groups include children with HIV infection, ado-

lescents with a history of multiple sexual partners, adolescents with a history of intravenous drug use and child victims of sexual assault. Screening for hepatitis C should be considered for children with risk factors for HCV and for pregnant women. The availability of safe regimens without IFN for adolescents older than 12 years and weighing > 35 kg makes them the best option in previously untreated and experienced patients, regardless of the severity of liver disease and the presence or absence of co-morbidities. Therefore, the combination of PEG IFN and ribavirin is no longer recommended. Chronic HCV infection is generally mild in children, but treatment should be an integral part of the public health approach necessary to succeed in the elimination of hepatitis C. The early identification of fibrosis in children may play a significant role in preventing the development of advanced liver disease. The non-invasive detection of paediatric cases with significant fibrosis progression can be very useful in treatment decisions. The results of available studies suggest that liver stiffness measurement methods and serum biomarker tests will help clinicians select paediatric patients with CHC who should undergo liver biopsy and can be used as a monitoring tool during follow-up.

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