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

*Giuseppe Indolfi, †Loreto Hierro, ‡Antal Dezsofi, §Jörg Jahnel, ||Dominique Debray, ¶Nedim Hadzic, #Piotr Czubkowski, **Girish Gupte, ††Yael Mozer-Glassberg, ‡‡Wendy van der Woerd, §§Françoise Smets, ||||Henkjan J. Verkade, and ||||¶¶Björn Fischler

ABSTRACT

Objectives: In 2017, the European Medicines Agency and the Food and Drug Administration approved the use of the fixed-dose combination of ledipasvir/sofosbuvir and of the combination of sofosbuvir and ribavirin for treatment of adolescents (12–17 years or weighing >35 kg) with chronic hepatitis C virus (HCV) genotype 1, 4, 5, and 6 and genotype 2 and 3 infections, respectively. Although trials with direct-acting antivirals are ongoing for younger children, the only available treatment in the United States and Europe for those <12 years is still the dual therapy of pegylated interferon and ribavirin. There is currently a lack of a systematic approach to the care of these patients. The Hepatology Committee of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition developed an evidence-based position paper for the management of chronic HCV infection in children.

Methods: A systematic literature search and meta-analysis were performed using MEDLINE and Embase from June 1, 2007 to June 1, 2017. The approach of the Grading of Recommendations Assessment, Development and Evaluation was applied to evaluate outcomes. European Society of Pediatric Gastroenterology, Hepatology and Nutrition Committee members voted on each recommendation, using the nominal voting technique.

Results: The efficacy of the different direct-acting antivirals combinations tested was higher, the relapse and the treatment discontinuation rates lower when compared to pegylated interferon and ribavirin.

Conclusions: This position paper addresses therapeutic management issues including goals, endpoints, indications, contraindications, and the optimal treatment regimen in children with chronic HCV infection.

Key Words: children, direct-acting antiviral, hepatitis C virus, meta-analysis, systematic review, treatment

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What Is Known

- Direct-acting antiviral drugs active against hepatitis C virus infection are highly effective and safe for treatment of adults with chronic hepatitis C virus infection.
- Pegylated interferon and ribavirin are no more recommended for treatment of adults.

What Is New

- The fixed-dose combination of sofosbuvir/ledipasvir and the combination of sofosbuvir and ribavirin have been recently approved for treatment of children 12 years or older or weighing >35 kg with chronic hepatitis C virus genotype 1, 4, 5, and 6 and 2 and 3 infection, respectively.
- Pegylated interferon and ribavirin are no more recommended for the treatment of children older than 12 years of age.

OBJECTIVES

The objectives of this position paper developed by the Hepatology Committee of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition are: to summarize the scientific evidence regarding treatment of chronic hepatitis C

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From the *Paediatric and Liver Unit, Meyer Children's University Hospital of Florence, Firenze, Italy, the †Pediatric Liver Service Hospital Infantil Universitario La Paz, Madrid, Spain, the ‡First Department of Paediatrics, Semmelweis University, Budapest, Hungary, the §Department of Pediatric and Adolescent Medicines, Medical University Graz, Graz, Austria, the ||Pediatric Centre, Hepatology, and Transplantation AP-HP, Hôpital Necker Enfants Malades, Paris, France, the ¶Paediatric Gastrointestinal, Liver and Nutrition Centre, Variety Children's Hospital, King's College Hospital, NHS Foundation Trust, Denmark Hill, Camberwell, London, UK, the #Department of Gastroenterology, Hepatology, Feeding Disorders and Pediatrics, The Children's Memorial Health Institute, Warsaw, Poland, the **Liver Unit (Including Small Bowel Transplantation), Department of Gastroenterology and Nutrition, Birmingham Children's Hospital, Steelhouse Lane, Birmingham, UK, the ††Schneider Children's Medical Center, Petah Tikva, Israel, the ‡‡Department of Pediatric Gastroenterology, Wilhelmina Children's Hospital, University Medical Centre Utrecht, Utrecht, The Netherlands, the §§UCL, Cliniques Universitaires Saint-Luc, Pediatric Gastroenterology and Hepatology, Brussels, Belgium, the ||||Department of Pediatrics, Center for Liver, Digestive, and Metabolic Diseases, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands, and the ¶¶Department of Paediatrics, Karolinska University Hospital, CLINTEC, Karolinska Institutet, Stockholm, Sweden.

Address correspondence and reprint requests to Dr Giuseppe Indolfi, Paediatric and Liver Unit, Meyer Children's University Hospital of Florence, Viale Gaetano Pieraccini 24, I-50139 Firenze, Italy (e-mail: giuseppe.indolfi@meyer.it).

virus (HCV) infection in children performing a systematic review and meta-analysis on the topic; to provide an extensive description of the state of the art of direct-acting antivirals (DAAs) development in children; to assess the actual and future role of IFN-based treatments and of IFN-free DAAs combinations in the current and future dynamic clinical environment; to provide consensus and recommendations on treatment of chronic HCV infection in children.

This position paper was developed to assist pediatricians and patients in the clinical decision-making of treating children with chronic HCV infection. Furthermore, it could assist policy makers in optimizing the development of new drugs for HCV-infected children.

BACKGROUND

The treatment perspective for HCV-infected patients has evolved substantially with the introduction of the first DAA-active against HCV in 2011. Nowadays, chronic HCV infection in adults is easy to treat. Ten different oral regimens have been licensed by European Medicines Agency (EMA) and the Food and Drug Administration (FDA) for treatment of adults with chronic HCV infection (Table 1). Each of these regimens can be used for achieving high (>90%) sustained virological response (SVR) rates in 12 weeks, independent of viral genotype, stage of fibrosis, and of co-infection with human immunodeficiency virus (HIV) (1–4). For certain populations, equally high SVR rates can be achieved by even shorter treatment durations, that is, 8 weeks.

The drugs currently licensed in Europe and United States for the treatment of chronic HCV infection in children, with age- and weight-specific limitations are IFN, pegylated interferon (PEG IFN), ribavirin and, recently, the fixed-dose combination of ledipasvir/sofosbuvir and sofosbuvir (Table 2). Few data are available on the pediatric use of DAAs and 8 trials are ongoing (Table 3). Although new treatments are expected to be approved for pediatric use for all age groups in the near future, there is uncertainty on the currently optimal approach to treat children with chronic HCV infection. Furthermore, there is concern as the timelines for the completion of the registration studies of the new drugs for children are far off (5,6).

Epidemiology of Hepatitis C Virus Infection in Children

The seroprevalence and burden of HCV infection in children are not well established. World Health Organization (WHO) recently estimated that in 2015, 71 million persons were living with HCV infection in the world (7). No pediatric data were provided in the WHO report (7). In a previous comprehensive review of the published literature on HCV epidemiology the global pediatric prevalence of anti-HCV was estimated at 11 million with 6 million viremic children (8). Preliminary results of a recent systematic review of HCV antibody seroprevalence in children, estimated that 13.2 (11.5–21.2) million children aged between 1 and 15 years are HCV infected worldwide (9). The prevalence of HCV was higher among children treated for malignancy, those with renal failure requiring hemodialysis and those who had undergone surgical procedures (10). Nowadays, vertical transmission from mother to the child is the main route of acquisition of HCV in childhood (11). In high-income countries, horizontal transmission through injection drug use has been described as an emerging and concerning route of acquisition of HCV in adolescents (12). On the other side, in low-income countries, iatrogenic transmission and transmission through traditional practices such as scarification and circumcision could account for the higher prevalence of the infection (13).

TABLE 1. Direct-acting antivirals against hepatitis C virus approved by the European Medicines Agency and the Food and Drug Administration in adults (date: August 2017)

Drug name	Producing company
Daclatasvir	BMS
Elbasvir/grazoprevir	MSD
Glecaprevir/pibrentasvir	Abbvie
Ledipasvir/sofosbuvir	Gilead
Ombitasvir/paritaprevir/ritonavir	Abbvie
Ombitasvir/paritaprevir/ritonavir/dasabuvir	Abbvie
Simeprevir	Janssen
Sofosbuvir	Gilead
Sofosbuvir/velpatasvir	Gilead
Sofosbuvir/velpatasvir/voxilaprevir	Gilead

Natural History of Hepatitis C Virus Infection in Children

Following vertical transmission of HCV, in the absence of treatment, 20% of the children clear the infection spontaneously, usually in the first 4 years of life, whereas the remaining 80% develops chronic infection that persists into adulthood (14–16). Chronic HCV infection is usually asymptomatic during childhood (14,15,17). Mild hepatomegaly was the only clinical finding reported in 10% of the children enrolled in a large, European, multicenter, prospective study of 266 infants born to HCV-infected mothers (15). In this cohort (15) and also according to the data of the largest pediatric observational study on chronic HCV infection (14), persistently raised alanine aminotransferase levels were observed in almost 50% of the children during follow-up. Extrahepatic manifestations of the infection that are potentially severe in adults (18), are rare in children (19) with the exception of subclinical hypothyroidism and autoimmune thyroiditis, described in 11% and 5.6% of HCV-infected children, respectively (20).

To date, when compared to adults, there is only limited amount of information concerning histopathology of the liver in children with chronic HCV infection (21). A wide spectrum of findings, ranging from no histopathological abnormalities to cirrhosis, have been described (17,22–31). The majority of the children presents a near normal liver histology after more than 2 decades of infection (22,23,25,31). Few children with advanced

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G.I. is investigator in a Gilead Sciences-sponsored clinical trial (*ClinicalTrials.gov* identifier: NCT02175758). L.H. participated as subinvestigator in ABBVIE's sponsored study on Ombitasvir, Paritaprevir, Ritonavir, Dasabuvir (M14-748 EudraCT 2015-000111-41). The remaining authors report no conflicts of interest.

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TABLE 2. Drugs approved by the European Medicines Agency and the Food and Drug Administration for treatment of children with chronic hepatitis C virus infection (date: August 2017)

Drug	Age, yr	Genotype	Dosage	Route of administration
Interferon α-2b	3–18	1–6	6×10^6 IU/m^2 3 times a week	Subcutaneous
Pegylated interferon α-2a	5–18	1–6	100 μg/m^2 per week	Subcutaneous
Pegylated interferon α-2b	3–18	1–6	1.5 μg/kg per week	Subcutaneous
Ribavirin	1–18	1–6	15 mg/kg per day in 2 divided doses	Oral
Sofosbuvir	12–17	2, 3	400 mg/day	Oral
Ledipasvir/sofosbuvir	12–17	1, 4–6	90/400 mg/day	Oral

liver disease have, however, been identified as young as 3 years and as early as 1-year postinfection (14,22).

Children tend to have more indolent HCV infection than adults. According to the results of the main studies on the topic, liver fibrosis slowly increases with the patient's age (17,23,24,28), the duration of the infection (23–25), and the severity of histological necroinflammation (22,23,28–30), although some studies failed to find these associations (22,30,32). The risk of cirrhosis in children suffering from chronic HCV infection is 1% to 4% while bridging fibrosis and severe inflammation were described in approximately 15% (14,15,17,22). Hepatocellular carcinoma is rare (14,22) with only 3 cases so far described (33,34). Comorbidities such as malignancy, hematological diseases with iron overload and viral coinfections (HIV and hepatitis B virus [HBV]), and alcohol consumption and obesity accelerate the development of severe liver disease (22,23).

Current Treatment for Children

Table 2 shows the drugs currently approved by the EMA and the FDA for treatment of children with chronic HCV infection, including their indications, age-specific limitations, dosage, and routes of administration. The fixed-dose combination of ledipasvir/sofosbuvir and the combination of sofosbuvir and ribavirin have been approved by FDA and EMA in April and June to July 2017, respectively. These drugs can be used for treatment of adolescents (12–17 years) or children weighing more than 35 kg with chronic HCV genotype 1, 4, 5, and 6 and genotype 2 and 3 infections, respectively. Children younger than 12 years in the United States and Europe can be treated with the dual therapy of PEG IFN α-2a or -2b and ribavirin. Children with HCV genotypes 1 or 4 infection should be treated for 48 weeks, whereas the ones with genotypes 2 or 3 should be treated for 24 weeks (21,35–38).

Direct-acting Antivirals

DAAs are classified into several categories, based on their molecular target: NS3/4A protease inhibitors, nucleotide and non-nucleotide inhibitors of NS5B polymerase, and NS5A inhibitors. The development of new combinations of DAAs is based on the concept that at least 2 drugs are needed to achieve the treatment goal of obtaining high virological response rates (>90%–95%) without selecting resistant mutants (39). When the backbone of the treatment is a nucleoside NS5B inhibitor (mainly sofosbuvir), only 1 other drug, an NS3/4A protease inhibitor or a NS5A inhibitor, is usually required. Conversely, a non-nucleoside NS5B inhibitor should be used together with both NS3/4A protease and NS5A inhibitors.

Standard of Care for Adults

Regimens evaluated in clinical trials and showing excellent efficacy (SVR in >90%–95% of treated patients) and good safety have been included in international guidelines. The American Association for the Study of Liver Disease/Infectious Disease Society of North America (ISDA), the European Association for the Study of Liver Disease, and the Asian Pacific Association for the Study of the Liver and the WHO issued and continuously update treatment guidance (1–4).

A recent Cochrane Group systematic review on DAAs showed the absence of a concrete effect of DAAs therapies in adults on complications related to chronic HCV infection such as hospitalization, liver deaths, and transplantations (40). Both the European Association for the Study of Liver Disease and American Association for the Study of Liver Disease /Infectious Disease Society of North America highlighted significant flaws in this analysis yielding misleading conclusions (41,42). These were mainly that the studies included in the review were not designed

TABLE 3. Ongoing studies with direct-acting antivirals in children and adolescents with chronic hepatitis C virus infection (last update September 2017)

Combined regimens	Genotype	Identifier	Expected completion
Glecaprevir/pibrentasvir	1–6	NCT 03067129	May 2022
Ombitasvir/paritaprevir/ritonavir ± dasabuvir ± ribavirin	1, 4	NCT 02486406	Sept 2019
Sfosbuvir + daclatasvir	4	NCT 03080415	June 2018
Ledipasvir/sofosbuvir*	1, 4	NCT 02868242	April 2019
Ledipasvir/sofosbuvir ± ribavirin	1, 4, 5, 6	NCT 02249182	July 2018
Sofosbuvir + ribavirin	2, 3	NCT 02175758	April 2018
Sofosbuvir/velpatasvir	1–6	NCT 03022981	Dec 2019
Gratisovir + ribavirin	1–6	NCT 02985281	June 2018

*Egyptian children undergoing cancer chemotherapy.

to determine the long-term benefits of treatment in adults which in fact could be highly significant.

METHODS

Recommendations were based on evidence resulting from a systematic revision and meta-analysis of existing articles on the topic published up to June 1, 2017. Evidence was evaluated by the authors and classified as high (A), moderate (B), or low (C) quality according to the Grading of Recommendations Assessment, Development and Evaluation system (43). The strength of recommendations in the Grading of Recommendations Assessment, Development and Evaluation system was classified as outlined in Supplemental Table A (Supplemental Digital Content, *http://links.lww.com/MPG/B238*). These recommendations are based on currently licensed drugs and will be updated, following approval of new drug regimens by the national and European regulatory agencies.

Systematic Review and Meta-analysis

A systematic literature search was conducted by 2 researchers (G.I., B.F.) working independently, in duplicate, using multiple keywords and standardized terminology in Medline, and EMBASE dating back to June 1, 2007 up to and through June 1, 2017 as reported in the Appendix 1 (Supplemental Digital Content, *http://links.lww.com/MPG/B238*). The following terms were used: ''hepatitis C virus''; ''children''; ''treatment''; and/or ''interferon''; and/or ''direct-acting antiviral'' with the limits English language, human species and ages from birth to 18 years. Conference abstracts from the 2015 to 2017 annual meetings of the European Association for the Study of Liver Disease, American Association for the Study of Liver Disease, European Society of Pediatric Gastroenterology, Hepatology and Nutrition, North American Society of Pediatric Gastroenterology, Hepatology and Nutrition, and of the European Society of Paediatric Infectious Disease were also evaluated.

Eligibility

Both randomized and open-label clinical trials assessing the efficacy of PEG IFN α-2a or PEG IFN α-2b in combination with ribavirin or of any DAA in children and adolescents (ages 3–18 years) with HCV infection were considered eligible. Eligible clinical trials had to provide a full treatment course to patients (48 weeks for HCV genotypes 1 and 4, or 24 weeks for HCV genotypes 2 and 3, and for DAAs 12–24 weeks independently of HCV genotype) and had to report the most significant data with regard to treatment (viral genotype, doses, SVR). Trials enrolling children coinfected with HIV and/or HBV or with comorbidities were excluded. We excluded observational or retrospective studies. Conference abstract data were excluded for IFN-based treatment as considered redundant and not affecting result of the meta-analysis, but were included for the newer DAAs combinations. The main reason for this was that some of the data available on the use of DAAs in children were up to June 1, 2017 still only available as abstracts. Abstracts were included if reporting on registered clinical trials on the use of DAAs in children; if the information contained was sufficiently clear and accurate to permit adequate comprehension and interpretation; and if the complete description of the design of the trial was available accessing *clinicaltrial.gov* using the registration number. Bibliographies of all relevant articles and of published systematic reviews were evaluated.

Study Selection

Two investigators (G.I. and B.F.) working independently, in duplicate, scanned all abstracts and obtained the full text reports of records potentially meeting the inclusion criteria. After obtaining full reports of the candidate studies, the same investigators independently assessed eligibility via full text review. Where required, a third investigator provided arbitration.

Data of Interest

Data were abstracted for SVR, relapse, and treatment discontinuations due to a lack of virological response, virological breakthrough, or to an adverse event.

Definitions

SVR was defined as undetectable HCV RNA 12 weeks (SVR12) or 24 weeks (SVR24) after treatment completion for DAAs or IFN-based regimes, respectively. Reappearance of HCV RNA in serum while still on therapy or after discontinuation of therapy were defined virological breakthrough and relapse, respectively.

Data Analysis

The inter-rater reliability on inclusion of articles was assessed using the phi statistic (ϕ). Pooled proportions were calculated for each data of interest using a Freeman-Tukey–type arcsine square root transformation, and applying a random-effects model. Sensitivity analyses assessed differences in the outcome of the 2 treatment combinations overall and by HCV genotypes (1 and 4; 2 and 3, respectively). Pooled confidence intervals for difference in proportions analyses were conducted to assess whether meaningful differences existed between these combinations. All analyses were conducted using MedCalc Statistical Software version 17.6 (MedCalc Software bvba, Ostend, Belgium; *http://www.medcalc.org*; 2017).

RESULTS

The schematic of study selection process is provided in Figure 1, whereas the complete results of the searches are described in the Appendixes 2 to 5 (Supplemental Digital Content, *http://links.lww.com/MPG/B238*). Overall, 16 studies met the inclusion criteria (35–38,44–55). The inter-rater reliability for study inclusion was high ($\phi = 1$).

Pegylated Interferon and Ribavirin

Eleven studies reporting on combined treatment with PEG IFN and ribavirin were included. The data of interest were reported in Supplemental Table B (Supplemental Digital Content, *http://links.lww.com/MPG/B238*). Overall, the efficacy of this combination therapy was higher for children infected by HCV genotypes 2 and 3 (90%; Table 4 and Fig. 2, panel A) than for those infected by genotypes 1 and 4 (48%; Table 4 and Fig. 2B). Relapse rate, independent from genotype and treatment duration, was 6% (Table 4). Treatment discontinuation was reported in 17% of the children treated (Table 4). Discontinuation due to severe adverse events occurred in 2%.

Direct-acting Antiviral

Two trials published as full-length articles and 3 as abstracts were included (Supplemental Table C, Supplemental Digital Content, *http://links.lww.com/MPG/B238*). The overall efficacy of the different DAAs combinations tested was high (98; Table 5 and

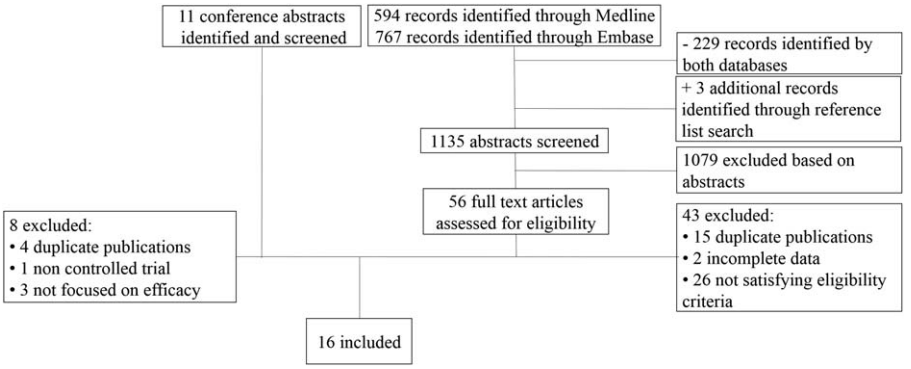

FIGURE 1. Flow chart of search results.

Fig. 3). Relapse rate was low (0.7%) and no treatment discontinuation was reported (Table 5).

Goal and Endpoint of Hepatitis C Virus Therapy

Independent of the treatment strategy used (PEG IFN and ribavirin or DAAs), the goal of therapy in children with chronic HCV infection is to cure the infection. The risk of HCV-related hepatic and extrahepatic complications in children is significantly lower than for adults. Advanced liver disease has been described in up to 4% of children with chronic infection in selected populations and could be prevented by curing HCV infection.

The endpoint of anti-HCV therapy is an SVR defined by undetectable HCV RNA in blood as assessed by a sensitive molecular method with a lower limit of detection (<15 IU/mL). SVR 12 weeks (SVR12) and/or 24 weeks (SVR24) after the end of treatment were used as endpoints in DAAs and in IFN-based studies, respectively. Adult data confirmed the high concordance between SVR12 and 24 (>99%) (56) and few long-term follow-up pediatric studies have shown that SVR24 corresponds to a definitive cure of HCV infection in 98% to 100% of cases (57,58). No long-term study (beyond 24 after the end of treatment) is presently available for DAAs in children.

Recommendation

- *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 blood by a sensitive assay (lower limit of detection ≤15 IU/mL) 12 weeks (SVR12) after the end of DAAs treatment or 24 weeks (SVR24) after the end of PEG IFN and ribavirin (A1).*

TABLE 4. Random-effects proportional meta-analysis of the data of interest assessed for children treated with pegylated interferon and ribavirin

Outcome	Proportion (95% confidence interval)	Number of arms
Sustained virological response		
Genotypes 1 and 4	48.6 (44.1–53.1)	11
Genotypes 2 and 3	90.9 (84.2–95.9)	7
Relapse	6.1 (2.8–10.5)	10
Virologic breakthrough	3.4 (0,8–7.7)	8
Treatment discontinuation	17.7 (6.4–33.2)	9
Due to lack of virologic response	14.9 (15.3–29.3)	9
Due to an adverse event	2.4 (1.1–4.3)	11

Indications for Treatment: Who Should Be Treated?

According to the currently available adult treatment guidelines (1–4) all treatment-naïve and -experienced patients with chronic HCV infection, independently of staging of liver disease, who are willing to be treated and who have no contraindications to treatment, should be considered for therapy. The timing of treatment in adult guidelines was impacted by the presence of significant fibrosis and cirrhosis, of extrahepatic manifestations or of comorbidities increasing the risk of rapid evolution of liver disease. Furthermore, treatment in adults is considered without delay in patients with HCV recurrence after liver transplantation and in those at risk of transmitting HCV. Adult guidelines changed significantly with the approval of the new DAAs combinations and indications for treatment are now based on the optimal safety and efficacy profiles irrespective of the costs that are the main limitation to the universal application of the new treatments.

The rationale underlying the indications for treatment of adults with chronic infection is valid also for children although the majority of them have a mild disease and do not need urgent treatment. In adults with chronic HCV infection assessment of liver disease severity is recommended before therapy (1,2). Noninvasive techniques are generally used as first line and liver biopsy is reserved for selected cases (1,2). Staging is highly relevant for adults, whereas it is less for children with chronic HCV infection as only a minority of them presents advanced liver disease. In children noninvasive techniques have not been validated yet and liver biopsy for obtaining liver tissue for histopathologic examination is still the criterion standard procedure for assessment of liver fibrosis (59). Although the presence of cirrhosis or advanced fibrosis affects the choice of the treatment regimen in adults, so far it has no effect in children where no alternative regimen is available. Liver stiffness measurement may replace in the future the use of liver histology for staging of HCV-related liver disease at least in adolescents. In the meantime, liver biopsy should be reserved for the few cases in which there is suspicion of advanced liver disease, potential additional etiologies or to confirm clinical evidence of cirrhosis (59).

Previous studies clearly demonstrated that both the physical and psychosocial health and cognitive functioning of asymptomatic children with chronic HCV infection are significantly reduced compared with children without HCV (60,61). Moreover, caregivers were highly distressed about their children's medical

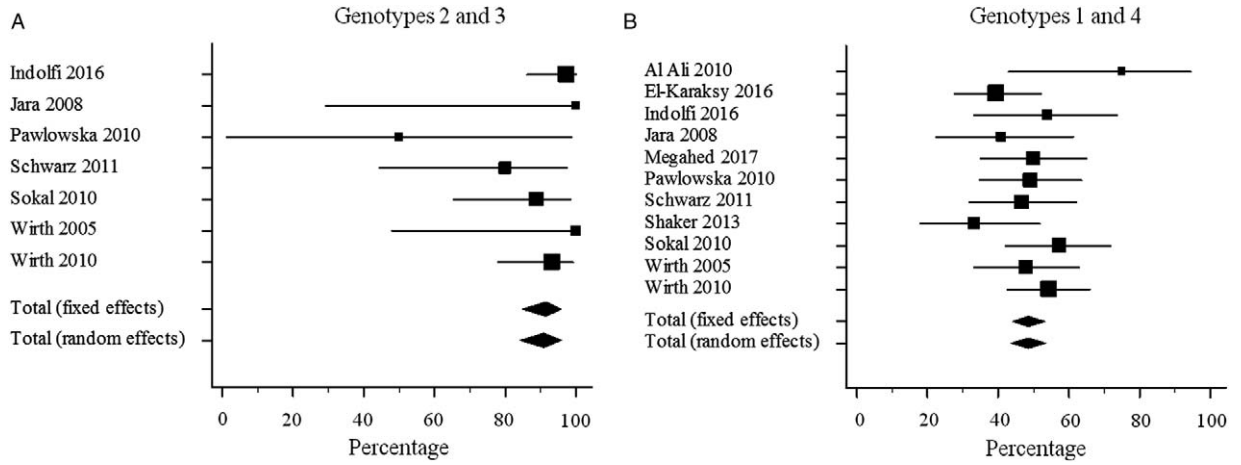

FIGURE 2. Meta-analysis results for sustained virological response in children infected with hepatitis C virus genotypes 2 and 3 (panel A) and 1 and 4 (panel B) treated with pegylated interferon and ribavirin. The study by Schwarz et al (49) was a prospective, randomized, controlled clinical trial; all the others were prospective, open-label and uncontrolled studies.

circumstances (61). Recently, it was demonstrated that adolescents treated with ledipasvir/sofosbuvir self-reported improvement of quality of life both during treatment and after achieving SVR that was confirmed by the parental assessment (62).

The cost of the new DAAs combination therapies have been an important obstacle to broader use of the treatment. The use of lower and therefore cheaper doses of DAAs in children when compared to adults could provide benefits in terms of potential cost savings. The recent data highlighting concerns about horizontal transmission of HCV infection in adolescents through injecting drug use in high-income settings provide additional evidence for supporting early treatment in children before they reach the age when this risk increases (63). This could also reduce the risk of sexual transmission of the infection.

Recommendations

- *The rationale underlying the indications for treatment of adults with chronic infection is valid also for children (B1).*
- *We recommend that 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 it should be evaluated case-to-case (A1).*

TABLE 5. Random-effects proportional meta-analysis of the data of interest assessed for children treated with direct acting antivirals

Outcome	Proportion (95% confidence interval)	Number of arms
Sustained virological response	98.1 (96.2–99.3)	5
Genotypes 1 and 4	98.2 (96.2–99.5)	4
Genotypes 2 and 3	96.9 (90.9–99.8)	2
Relapse	0.7 (0.08–1.9)	5
Virologic breakthrough	not calculable	5
Treatment discontinuation	not calculable	5
Due to lack of virologic response	0	0
Due to an adverse event	0	0

- *We recommend that treatment is considered without delay in presence of significant fibrosis and cirrhosis, extrahepatic manifestations and co-morbidities increasing the risk of rapid evolution of liver disease (solid organ or hematopoietic stem cell transplant recipients, other patients undergoing immunosuppressive treatments) (A1).*
- *Treatment can be generally deferred in age-cohorts where combined PEG IFN and ribavirin is the only treatment option (C1).*

Approved Drugs in Europe in 2017

Two different DAAs combinations for treatment of children with chronic HCV infection have so far been approved by the EMA and FDA, namely the fixed-dose combination of ledipasvir/sofosbuvir and of sofosbuvir and ribavirin. Both therapy combinations can be used in Europe only for children older than 12 years who are chronically infected by HCV genotypes 1 or 4 and 2 or 3, respectively. FDA approved the use of the two regimens also for children weighing at least 35 Kg. EMA approved the use of ledipasvir/sofosbuvir and sofosbuvir under the centralized authorization procedure. This procedure allows pharmaceutical companies to market the medicines throughout the European Union on the basis of a single marketing authorization although the synchronous availability of the drug in each Member State is not granted. Decisions about price and reimbursement depend on the potential role and use of the medicine in the context of the national health system and take place at a country level. The differences in the health systems across Europe together with the cost of the new drugs could result in the nonhomogeneous access of DAAs in different European countries. One of the major aims of the present position paper is to assist national and international regulatory agencies in speeding up and facilitating the availability of the drugs for this specific target population.

The therapeutic superiority of the new DAAs regimens when compared with the IFN-based ones in terms of efficacy couples with the better safety profile. A detailed description of the safety profile of IFN-based therapies is available elsewhere (64). The analysis of treatment discontinuation rates both for virological nonresponse/breakthrough and for adverse events related to therapy confirmed the safety of DAAs and the burdensome safety profile of PEG IFN and ribavirin. It is well known that children have a better tolerance to IFN and ribavirin than adults and

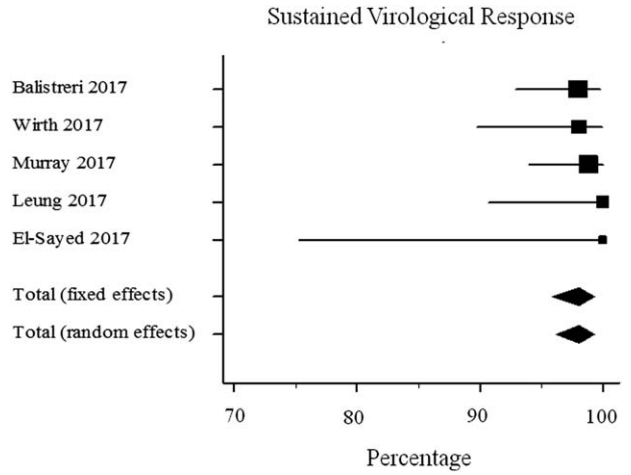

FIGURE 3. Meta-analysis results for sustained virological response in children infected with hepatitis C virus (all genotypes) treated with direct acting antivirals. All the clinical trials evaluated were prospective, open-label and uncontrolled.

that the treatment discontinuation rate due to adverse events related to therapy is not a good indicator of the safety of the treatment. Both on-therapy side effects, such as flu-like symptoms including fever, decreased appetite, asthenia, and fatigue and hematological complications such as anemia, leucopenia, and neutropenia, and possible irreversible after-therapy side effects, such as thyroid disease, diabetes, ophthalmologic complications, and impairment of growth (37,38,57,65), should be considered when assessing the risk-benefit profile of PEG IFN and ribavirin therapy in children with HCV infection.

Patients Group 1: Treatment of Chronic Hepatitis C Virus Infection in Adolescents

The availability of safe IFN-free regimens for adolescents older than 12 years or children weighing >35 kg, makes these the best options in treatment-naïve and experienced patients independent of the stage of liver disease and of the presence or absence of comorbidities. Consequently, the combination of PEG IFN and ribavirin is no more recommended. The cost of the new drugs and the differences in the health systems across Europe could be responsible for the nonhomogeneous use of DAAs in different countries and regions. It is hoped that the publication of the present up-to-date position paper will assist national and international regulatory agencies and industry in setting up specific reimbursement schedules and discounting drug costs for this specific target population.

Recommendations

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

Panel: Recommendations for Treatment of Chronic HCV infection in Children

- The goal of therapy in children is to cure HCV infection to prevent the potential progression of HCV-related liver disease and its complications (A1).
- The endpoint of therapy in children is undetectable HCV RNA in blood by a sensitive assay (lower limit of detection ≤15 IU/ml) 12 weeks (SVR12) after the end of DAAs treatment or 24 weeks (SVR24) after the end of PEG IFN and ribavirin (A1).
- The rationale underlying the indications for treatment of adults with chronic infection is valid also for children (B1)
- We recommend that 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 it should be evaluated case-to-case (A1)
- We recommend that treatment is considered without delay in presence of significant fibrosis and cirrhosis, extrahepatic manifestations and co-morbidities increasing the risk of rapid evolution of liver disease (solid organ or haematopoietic stem cell transplant recipients, other patients undergoing immunosuppressive treatments) (A1)
- Treatment can be generally 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) independently of the stage of liver disease and of co-morbidities (C1).
- PEG IFN and ribavirin are presently no more recommended for treatment of HCV-infected adolescents since 2017 (C1).
- We recommend that children older than 12 years or who weigh > 35 kg chronically infected with HCV genotype 1 or 4, are treated with the combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with a single tablet administered once daily for 12 weeks (C1The recommended duration of therapy for treatment-experienced children with HCV genotype 1 infection and with compensated cirrhosis is 24 weeks (C2).
- We recommend that children older than 12 years or who weigh >35 Kg chronically infected with HCV genotype 2 are treated with sofosbuvir 400 mg once daily and weight-based ribavirin (15 mg/Kg in two divided doses) for 12 weeks (C1)
- We recommend that children older than 12 years or who weigh >35 Kg chronically infected with HCV genotype 3 are treated with sofosbuvir 400 mg once daily and weight-based ribavirin (15 mg/Kg in two divided doses) for 24 weeks (C1)
- We no longer recommend PEG IFN and ribavirin as a general treatment for children younger than 12 years 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)

FIGURE 4. Panel: recommendations for treatment of chronic HCV infection in children. DAA = direct-acting antiviral; HCV = hepatitis C virus; PEG IFN = pegylated interferon; SVR = sustained virological response rate.

- *PEG IFN and ribavirin are presently no more recommended for treatment of HCV-infected adolescents since 2017 (C1).*

Treatment of Hepatitis C Virus Genotype 1 or 4 Infection

Only the fixed dose combination of ledipasvir/sofosbuvir is available for adolescents with HCV genotype 1 or 4 in 2017.

In the recently published registration trial, 100 patients have been enrolled and treated with the combination of ledipasvir (90 mg) and sofosbuvir (400 mg) as a single tablet administered once daily for 12 weeks (51). This prospective, open-label, uncontrolled study included 80 treatment-naïve, 1 patient with and 42 without cirrhosis, respectively and 57 patients in whom the degree of fibrosis was unknown. SVR was achieved in 98% (98/100) of cases after 12 weeks of treatment. The 2 patients who did not achieve SVR12 were lost to follow-up, 1 at treatment week 4, the other after having achieved end of treatment virological response. The most commonly reported adverse events were headache (27%), diarrhea (14%), and fatigue (13%), all being reversible after the treatment completion (51). None had severe adverse events and significant abnormalities in laboratory results. No data are currently available on possible shortening of the treatment to eight weeks as suggested in adults if their baseline HCV RNA level is <6 million (6.8 Log) IU/mL (66). In this trial, children with HCV genotype 1 infection, who were treatment experienced with compensated cirrhosis were supposed to be treated for 24 weeks but no child with such characteristics was enrolled. The EMA- and FDA-approved duration of therapy with ledipasvir/sofosbuvir for treatment-experienced, cirrhotic children with HCV genotype 1 infection is 24 weeks.

Recommendation

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

Treatment of Hepatitis C Virus Genotype 2 or 3 Infection

Only one IFN-free treatment option, the association of sofosbuvir and ribavirin, is currently available for adolescents infected with HCV genotype 2 or 3. In the recently published prospective, open-label, uncontrolled registration trial, 52 patients have been enrolled and treated with sofosbuvir 400 mg once daily and weight-based ribavirin (15 mg/kg) twice daily for 12 (genotype 2) or 24 (genotype 3) weeks (52). Forty-three (83%) of the patients were treatment-naïve and 21 patients underwent liver biopsy showing the absence of cirrhosis. SVR12 was achieved in 98% (51/52) of cases and was 100% (13/13) for patients with genotype 2 and 97% (38/39) for genotype 3. The remaining patient was lost to follow-up after achieving SVR 4 weeks after the end of treatment and thus did not achieve SVR12. The most commonly reported reversible adverse events were nausea (27%) and headache (23%) (52).

Despite the good efficacy rate of the combined therapy with PEG IFN and ribavirin in children with chronic HCV infection (SVR24 in 90% of the children treated for 24 weeks), given the higher efficacy rate and the better safety profile of sofosbuvir and ribavirin, PEG IFN and ribavirin are no more recommended. It should be noted that the association of sofosbuvir and ribavirin is no more considered as standard of care for treatment of adults with HCV genotype 2 or 3, because other combinations, avoiding ribavirin, are available (1–4). Hopefully, in the future until new ribavirin-free options will be available also for children substituting the association of sofosbuvir and ribavirin.

Recommendations

- *We recommend that children older than 12 years or who weigh >35 kg chronically infected with HCV genotype 2 are treated with sofosbuvir 400 mg once daily and weight-based ribavirin (15 mg/kg in 2 divided doses) for 12 weeks (C1).*
- *We recommend that children older than 12 years or who weigh >35 kg chronically infected with HCV genotype 3 are treated with sofosbuvir 400 mg once daily and weight-based ribavirin (15 mg/kg in 2 divided doses) for 24 weeks (C1).*

Patients Group 2: Treatment of Chronic Hepatitis C Virus Infection in Children Younger Than 12 Years

No IFN-free treatment option is yet available for children younger than 12 years infected with HCV. There is uncertainty about how to manage these children. In the past, most of the children who received the therapy were treated independently of the stage of HCV-related liver damage to cure the infection and prevent the unpredictable progression of the disease. On the contrary, the majority of the infected children did not receive treatment given the overall mild nature of HCV-related liver disease, the low efficacy of PEG IFN with ribavirin (especially for genotypes 1 and 4) and its burdensome safety profile. At present, the latter approach is even more justified, given the results of the DAAs combinations in older pediatric age cohorts and the preliminary results of the fixed-dose combination of ledipasvir/sofosbuvir in children aged 6 to 11 years (53). In this prospective, open-label, uncontrolled trial 90 patients had been enrolled and all were treated with ledipasvir (45 mg) and sofosbuvir 200 mg once daily with a single tablet administered once daily for 12 weeks, except 1 genotype 1 treatment-experienced cirrhotic patient and 2 genotype 3 patients, who received 24 weeks of therapy. Eighty-six (96%) of the patients were infected by HCV genotype 1, and 2 each (2%) by HCV genotype 3 and 4. Eighteen (20%) were treatment-experienced and 2 had cirrhosis. Ninety-nine percent (89/90) of the children treated achieved SVR12. One genotype 1a patient with cirrhosis relapsed at fourth follow-up visit. The most commonly reported adverse events were headache (19%), fever (17%), and abdominal pain (15%) (53).

In most cases treatment of children younger than 12 years could be postponed until the expected extension to the existing age indication for DAAs is granted. It is possible that the treatment could be warranted in isolated cases when there is a high clinical suspicion of advanced liver disease that is confirmed by a liver biopsy showing significant fibrosis (14,22,23,30). Such cases should be referred to a centre with experience in the treatment of children with chronic HCV infection and possible off-label use of DAAs should be considered.

Recommendation

- *We no longer recommend PEG IFN and ribavirin as a general treatment for children younger than 12 years 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 comorbidities. These cases should be referred to a center with experience in the treatment of children with chronic HCV infection and the possible off-label use of DAAs could be considered (C1).*

Treatment of Special Groups

No data from controlled trials are available on the use of DAAs in children with coinfections (HBV, HIV), comorbidities (renal impairment, nonhepatic solid organ transplant recipients, children before and after liver transplantation, active drug users, patients with hemoglobinopathies and coagulation disorders) and nonsustained virological responders to DAAs. Isolated and highly promising experiences with young children undergoing liver transplantation or with cirrhosis are available (67,68). There is an ongoing debate as to whether adults with decompensated cirrhosis without hepatocellular carcinoma awaiting liver transplantation should be treated for their HCV infection before or after liver transplantation. The suggested approach is to initiate treatment as soon as possible to complete a full treatment course before transplantation (1,2). The positive effect of viral clearance on liver function may lead to delisting selected cases. When the patient is listed for liver transplantation and the expected waiting time is shorter than the duration of the full DAAs treatment course there is indication to make the transplant first and treat for HCV promptly after transplantation (1,2). In adults with HCV recurrence after liver transplantation treatment with DAAs is considered without delay (1,2). Similar approaches seem reasonable for children with decompensated cirrhosis without hepatocellular carcinoma awaiting or having undergone liver transplantation.

Perspective of New Treatments

At least 1 other treatment regimen (ombitasvir/paritaprevir/ritonavir with or without dasabuvir with or without ribavirin) for children older than 12 years of age is at the clinical developmental stage. In the recently presented prospective, open-label, uncontrolled ZIRCON trial, 38 patients with HCV genotypes 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) (54). All the patients received 12 weeks of treatment with the exception of 1 patient with HCV genotype 1a infection with cirrhosis who was treated for 24 weeks. Twenty-five (66%) of the patients were treatment-naïve and 37 (97%) were noncirrhotic. All 38 patients achieved SVR12 (100%). The most commonly reported adverse events were headache (21%) and asthenia (18%) (54).

Recently, preliminary data from a prospective, open-label, uncontrolled trial on the 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. SVR was 100% (Supplemental Table C, Supplemental Digital Content, *http://links.lww.com/MPG/B238*) (55).

CONCLUSIONS

The fixed-dose combination ledipasvir/sofosbuvir and sofosbuvir used with ribavirin are safe and effective and are the best options for treatment of chronic HCV infection in adolescents. Despite the overall impressive results already obtained, it should be noted that the major conclusions and recommendations of the present position paper are based on a small number of trials of DAAs, all with a short follow-up. This should be accounted for as a major limitation and the availability of more studies and of the long-term follow-up data is needed to confirm the present results. However, the existing adult long-term experience with DAAs is highly encouraging.

Drug development continues and these recommendations will need to be updated regularly, following approval of new drug regimens by the EMA. The next generation, ribavirin-free, DAA combinations (ie, sofosbuvir/velpatasvir and glecaprevir/pibrentasvir) demonstrate high pan-genotypic efficacy with shorter duration of treatment while maintaining the highest safety profiles. This is particularly relevant for HCV genotype 3 infection where sofosbuvir and ribavirin is no more a recommended regimen in adults.

The present position paper advocates 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. Chronic HCV infection has overall a benign course in children but treatment should be an integral component of the public health approach needed for success in moving toward eradication of hepatitis C.

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