Treatment of Adolescents With Chronic Hepatitis C Virus Infection: New Regimen on the Block

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In 2011 boceprevir and telaprevir, two NS3/4A protease inhibitors belonging to the first generation of direct-acting antiviral agents (DAAs) were approved in combination with pegylated interferon and ribavirin for treatment of adults with chronic hepatitis C virus (HCV) infection. The triple therapy with boceprevir or telaprevir showed improved response rates when compared with the dual therapy with pegylated interferon and ribavirin, but was accompanied by significant side effects. Since 2011, the U.S. Food and Drug Administration and the European Medicines Agency have approved 13 different DAAs and 6 all-oral, interferon-free, highly effective and safe fixed-dose combinations for the treatment of adults with chronic HCV infection (elbasvir/grazoprevir, glecaprevir/pibrentasvir, ombitasvir/paritaprevir/ritonavir, sofosbuvir/ledipasvir, sofosbuvir/velpatasvir, and sofosbuvir/velpatasvir/voxilaprevir). Six years later, between April and July 2017, the U.S. Food and Drug Administration and the European Medicines Agency approved the use of sofosbuvir/ledipasvir for adolescents (ages 12 years or older) with HCV genotype 1, 4, 5, or 6 infection and sofosbuvir in combination with ribavirin for those with HCV genotype 2 or 3 infection (Fig. 1).

Regulatory authorities need clinical trials to reach their opinions on the authorization of medicines. Although a number of industry-driven clinical trials on the use of DAAs have been completed for adults, according to clinicaltrials.gov, only 2 (the sofosbuvir/ledipasvir trial [NCT 02249182] and the sofosbuvir plus ribavirin trial [NCT 02175758]) of the 7 ongoing industry-driven clinical trials in children (ages 3-17 years) are close to the estimated study completion date (August and September 2018, respectively). So far, results from specific age cohorts enrolled have been published. The safety and efficacy of sofosbuvir/ledipasvir for children (ages 6-11 years)[1] and adolescents (ages 12-17 years),[2] and sofosbuvir and ribavirin for adolescents,[3] have been reported recently. In addition to industry-driven clinical trials, few investigator-initiated studies are available on the use of DAAs in children and adolescents with chronic HCV infection.[4-7]

In Hepatology Communications, Leung et al.[8] reported the preliminary results of the ZIRCON study (NCT 02486406). This study is currently ongoing and is investigating a regimen including three DAAs—paritaprevir (an NS3/4A inhibitor) co-administered with ritonavir, ombitasvir (an NS5A inhibitor), and dasabuvir (a nonnucleoside NS5B inhibitor)—with or without ribavirin in children ages 3-17 years with chronic HCV infection. Leung et al. evaluated

Abbreviations: DAAs, direct-acting antiviral agents; HCV, hepatitis C virus; SVR12, sustained virological response 12 weeks after the end of treatment.

Received August 31, 2018; accepted September 6, 2018.

View this article online at wileyonlinelibrary.com.
DOI 10.1002/hep4.1261

Potential conflict of interest: Nothing to report.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Giuseppe Indolfi
Pediatric and Liver Unit
Meyer Children's University Hospital of Florence
Viale Gaetano Pieraccini 24
Firenze I-50139, Italy
E-mail: giuseppe.indolfi@meyer.it
Tel: +39-055-5662480
Fax: +39-055-56621

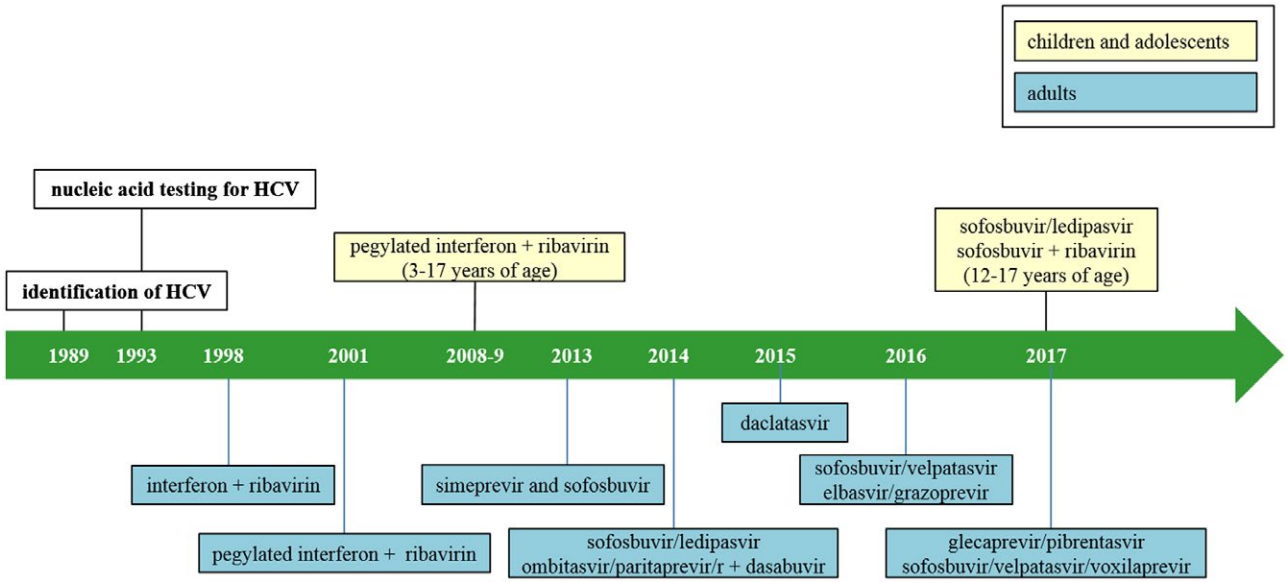

FIG. 1. Milestone in HCV research for children and adults.

the efficacy and safety of this regimen in 38 adolescents (ages 12-17 years), with (n = 1) or without compensated cirrhosis, who were either previously untreated or unsuccessfully treated with peginterferon and ribavirin (n = 13). Consistent with adult label indications, patients without cirrhosis with HCV genotype 1 infection received paritaprevir/ritonavir, ombitasvir, and dasabuvir for 12 weeks; ribavirin was added to those infected with HCV subtype 1a and treatment was prolonged for 24 weeks if compensated cirrhosis was present. None of the adolescents enrolled with HCV genotype 1b had cirrhosis, and the expected duration of treatment for this group was 12 weeks without ribavirin. Adolescents with HCV genotype 4 infection received paritaprevir/ritonavir, ombitasvir, and ribavirin for 12 weeks. According to the protocol, patients received 1 to 5 pills per day (paritaprevir/ritonavir/ombitasvir once daily ± dasabuvir twice daily ± ribavirin twice daily) for 12 to 24 weeks. Sustained virological response 12 weeks after the end of treatment (SVR12) was achieved by all of the patients. The safety profile of the regimen was excellent with no grade 3 adverse event and no treatment discontinuation.[8]

So, what have we learned from the ZIRCON study and from the results of the other clinical trials on the use of DAAs in children and adolescents with chronic HCV infection? First, across the different studies the adult dosing for adolescents and, for sofosbuvir and ledipasvir, half the dose used in adults for children ages 6-11 years, resulted in comparable plasma exposures to those found in the phase II and phase III clinical trials in adults with chronic HCV infection.[1-3] Second, all of the studies showed excellent efficacy (SVR12) in children and adolescents with chronic HCV infection independently of age, treatment history, degree of liver fibrosis, and treatment duration.[1-3] Third, the safety profile of these treatments was excellent in children and adolescents.[1-3]

At this juncture, there are still gaps to fill and we are certainly not ready to close the book on the treatment of chronic HCV infection in children and adolescents. No data are currently available on the use of DAAs in children younger than 6 years. This is an interesting age cohort in which the effect of compliance with treatment administration could be relevant, although it is difficult to expect any real difference with older children in terms of safety and efficacy. Only a small number of pediatric trials of DAAs, all with a short follow-up, are available. The availability of more studies and the long-term follow-up data are needed to confirm the existing results; however, the adult's longer-term experience with DAAs is highly encouraging.

It is remarkable how fast the progress in drug discovery has been in recent years, how fast the approval

has been for adults with chronic HCV infection, and—in comparison—how delayed it is for children and adolescents (Fig. 1). For example, no data are available for children and adolescents for the pangenotypic DAAs combination regimens, including the new fixed-dose combinations sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/voxilaprevir and glecaprevir/pibrentasvir, which are the current standard of care for adults with chronic HCV infection according to the most recently updated recommendations for treatment,[9-11] and few preliminary results have been reported for sofosbuvir/daclatasvir, which is used commonly in low-income and middle-income countries.[5,6] These drugs achieve high treatment efficacy across all six major HCV genotypes, including patients with cirrhosis or human immunodeficiency virus coinfection. Pangenotypic DAAs combinations, reducing the need for genotyping, simplify the pathway of care and facilitate the availability and the expansion of treatment worldwide—especially in the geographic areas where the burden of the infection is higher.[10] Furthermore, as an added benefit, adherence with medication regimens, a key element in the achievement of treatment response, can be improved by the use of fixed-dose combination products. This latter aspect is crucial for children and is also relevant to the regimen with paritaprevir/ritonavir, ombitasvir, and dasabuvir with or without ribavirin, in which some children (i.e., those infected with HCV subtype 1a with compensated cirrhosis) are supposed to receive 5 pills per day for 24 weeks.

Shortening the treatment duration from 12 to 8 weeks has been demonstrated to be possible for specific DAAs combinations in adults, based on studies aimed at identifying baseline and on-treatment predictive factors. The absence of cirrhosis is the key limiting condition for the use of sofosbuvir/ledipasvir and glecaprevir/pibrentasvir for 8 weeks.[9,11] Chronic HCV infection in children is usually associated with a mild disease and cirrhosis, across different pediatric studies, has been described in 2% of the cases.[12] It is possible and likely that most of the children with chronic HCV infection could benefit from a shorter duration of treatment. A pilot Egyptian study evaluated in 10 consecutive adolescents with HCV genotype 4 infection the efficacy of sofosbuvir and daclatasvir for a response-tailored duration of 8 weeks for those who achieved very rapid virologic response (vRVR), defined as undetectable HCV RNA in serum at treatment week 2.[7] All of the patients achieved vRVR, were treated for 8 weeks, and achieved SVR12.[7] Further studies are needed to confirm these promising preliminary results. Again, although the effect of a shorter treatment duration could be limited in high-income countries where the prevalence of the infection is usually low, it could be relevant in low-income and middle-income countries where the prevalence of HCV is high.

In conclusion, the study by Leung et al. is important as it paves the way for the possible approval by the U.S. Food and Drug Administration and the European Medicines Agency of paritaprevir/ritonavir, ombitasvir, and dasabuvir with or without ribavirin for use in adolescents with chronic HCV genotype 1 or 4 infection, and could provide clinicians and patients with an effective alternative regimen. For adults, the availability of drugs from different companies resulted not only in lowering the price of these expensive medicines, but more importantly, also improved access to treatment. As soon as the combination of paritaprevir/ritonavir, ombitasvir, and dasabuvir with or without ribavirin is approved for adolescents, it will be important that recommendations for treatment issued by the major international scientific societies be updated to include the new regimen. Consistency in indications for treatment and in selection of DAAs regimens across the different authorities would simplify the treatment and broaden the number of children who get treatment worldwide, but so far has been difficult to achieve.

Giuseppe Indolfi
Silvia Ricci
Pediatric and Liver Unit
Meyer Children's University Hospital of Florence
Firenze, Italy

REFERENCES

1) Murray KF, Balistreri WF, Bansal S, Whitworth S, Evans HM, Gonzalez-Peralta RP, et al. Safety and efficacy of ledipasvir-sofosbuvir with or without ribavirin for chronic hepatitis C in children ages 6-11. Hepatology. In press.
2) Balistreri WF, Murray KF, Rosenthal P, Bansal S, Lin CH, Kersey K, et al. The safety and effectiveness of ledipasvir-sofosbuvir in adolescents 12-17 years old with hepatitis C virus genotype 1 infection. Hepatology 2017;66:371-378.
3) Wirth S, Rosenthal P, Gonzalez-Peralta RP, Jonas MM, Balistreri WF, Lin CH, et al. Sofosbuvir and ribavirin in adolescents 12-17 years old with hepatitis C virus genotype 2 or 3 infection. Hepatology 2017;66:1102-1110.

4) Indolfi G, Serranti D, Resti M. Direct-acting antivirals for adolescents with chronic hepatitis C. Lancet Child Adolesc Health 2018;2:298-304.
5) El-Shabrawi MH, Abdo AM, El-Khayat HR, Yakoot M. Shortened 8 weeks course of dual sofosbuvir/daclatasvir therapy in adolescent patients, with chronic hepatitis C infection. J Pediatr Gastroenterol Nutr 2018;66:425-427.
6) Yakoot M, El-Shabrawi MH, AbdElgawad MM, Mahfouz AA, Helmy S, Abdo AM, et al. Dual sofosbuvir/daclatasvir therapy in adolescent patients with chronic hepatitis C infection. J Pediatr Gastroenterol Nutr 2018;67:86-89.
7) El-Shabrawi MHF, Kamal NM, El-Khayat HR, Kamal EM, AbdElgawad M, Yakoot M. A pilot single arm observational study of sofosbuvir/ledipasvir (200 + 45 mg) in 6- to 12- year old children. Aliment Pharmacol Ther 2018;47:1699-1704.
8) Leung DH, Wirth S, Yao B, Viani RM, Gonzalez-Peralta R, Jonas MM, et al. Ombitasvir/paritaprevir/ritonavir with or without dasabuvir and with or without ribavirin for adolescents with HCV genotype 1 or 4. Hepatol Commun 2018;2:1311-1319.
9) AASLD-IDSA. HCV guidance: recommendations for testing, managing, and treating hepatitis C. https://www.hcvguidelines.org. Accessed 30, August 2018.
10) World Health Organization. Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection. Geneva, Switzerland: World Health Organization; 2018.
11) European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C 2018. J Hepatol 2018;69:461-511.
12) Indolfi G, Guido M, Azzari C, Resti M. Histopathology of hepatitis C in children, a systematic review: implications for treatment. Expert Rev Anti Infect Ther 2015;13:1225-1235.