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EDITORIAL

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Hepatitis C virus therapy in children: No one should be left behind

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Hepatitis C Virus (HCV) infects approximately 184 million people worldwide, with a greater prevalence in certain geographical areas such as Central and East Asia, Northern Africa and the Middle East, where its prevalence may be greater than 3.5% of the population.[1,2] Chronic hepatitis caused by HCV infection is associated with the development of complications of liver disease such as liver failure and development of hepatocellular carcinoma – although these complications tend to develop late in the course of the disease – and successful treatment of HCV infection is associated with the abolishment of the likelihood of liver disease progression as well as with a dramatic decrease in the rate of development, or recurrence, of primary liver cancer and the need for liver transplantation.[3-6] In this regard, the recent advent of highly efficacious direct-acting antivirals (DAA) has radically modified the therapeutic scenario for patients with chronic HCV infection as they allow the treatment of all the categories of patients, independently of disease severity, presence of comorbidities and viral characteristics, and are able to ensure the viral cure in virtually all treated patients.[7]

From a global point of view, the World Health Organisation (WHO) recently set the ambitious goal to drastically decrease, by 2030, chronic hepatitis viruses infection to 0.9 million and to reduce the annual deaths from chronic hepatitis to less than 0.5 million, with the ultimate objective of eliminating viral hepatitis as a major public health threat.[8] In this regard, besides striving to identify all infected patients in the general population and link them to care and treatment, one of the strategic health objectives is to identify well-characterised populations, who often share modality of HCV acquisition and who are already in care as a result of peculiar comorbid conditions, or demographical or social features, where the goal of HCV "eradication", rather than its confinement, can actually be obtained.[9,10] Such populations are represented by patients affected by chronic kidney disease who are on haemodialysis, transfusion-dependent thalassaemic patients, people living with the human immunodeficiency virus, people who use drugs and children.[11] In these particular groups of patients eradication of HCV infection has a multifold perspective: it allows treating all patients with a given condition, or demographical characteristic, in a reasonably limited period of time, drastically reducing the likelihood of further diffusion of infection within the same communities; it portends an added benefit provided by HCV clearance to the therapeutic management of comorbid conditions; and in the paediatric setting it not only improves the projected health benefit in an otherwise healthy population by eliminating the potential for chronic liver disease progression and the development of associated conditions but also frees young patients from the social and psychological stigmata of a transmissible disease.[12-15]

Egypt is the country with the highest prevalence of HCV infection in the world, and despite a recent decrease in the prevalence of infection of approximately 30% – a finding mainly owing to ageing of the cohort initially infected in the '60s that represented the majority of chronic hepatitis C patients in the country – the prevalence of HCV RNA positivity in children aged 1-14 is as high as 0.2%.[16] According to the only and yet unpublished systematic review of the prevalence of HCV viraemia in adolescents and children based on studies from 102 countries, 19 countries accounted for 80% of worldwide infections and Egypt was confirmed as one of the countries with the highest paediatric prevalence of HCV infection in the world.[17] To achieve the goal of the global strategy for elimination of HCV infection as a public health threat, inclusion of all affected populations, including children and adolescents is required. A mass scale-up of testing and treatment in children is needed, particularly in low- and middle-income countries (LMICs) where the burden of the disease is at the highest.[18] Egypt is the only country addressing access to the HCV cascade of care on a nationwide basis with inclusion of school children, 12 years and above and/or more than 35 kg, in a test-and-treat programme fully funded by the state and national insurance service.

To date, few paediatric clinical trials on the use of DAA regimens, conducted primarily in a few high-income countries, have been completed and published[19-24]; isolated results from real-world experiences are available but no long-term follow up on the use of these drugs is available. In the present issue of Liver International, Kamal and collaborators described in a pilot study the safety and the efficacy of sofosbuvir/ledipasvir (tablet 200/45 mg) for the treatment of chronic, genotype 4 HCV infection in 22 children aged 3-6 years.[25] Eleven children were randomly assigned to receive 8 weeks of treatment while the remaining were treated for 12 weeks. Sustained virological response at week 12 following treatment (SVR_{12}) was 100%, no serious adverse event was reported and none of the children discontinued the treatment because of an adverse event. The results of the study by Kamal and collaborators confirm the efficacy and the safety of sofosbuvir/ledipasvir in children between 3 and 6 years of age. Furthermore, the study demonstrates that this combination is efficacious for HCV

TABLE 1 Direct-active antiviral regimens approved for treatment of chronic hepatitis C virus infection in children and adolescents

Regimen	Genotype (GT) & duration of treatment	Formulations	Doses
Sofosbuvir/ledipasvir	- GT 1, 4, 5, 6:12 wk - GT 1, treatment-experienced, cirrhosis: 24 wk	- Tablet (fixed-dose combination, FDC) 400/90 mg - Tablet (FDC) 100/22.5 mg - Packet of granules 50/11.25 mg	- 12-17 y: 400/90 mg/d - 6-11 y: 200/45 mg/d - 3-5 y: 200/45 mg/d if ≥17 kg; 150/33.75 mg/d if <17 kg
Sofosbuvir + ribavirin	- GT 2:12 wk - GT 3:24 wk	Sofosbuvir - Tablet 400 mg - Tablet 100 mg - Capsules 50 mg containing granules	Sofosbuvir - 12-17 y: 400 mg/d - 6-11 y: 200 mg/d - 3-5 y: 200 if ≥17 kg; 150 mg/d if <17 kg Ribavirin - 15 mg/Kg/d in two divided doses
Glecaprevir/ pibrentasvir	- All GTs: 8 wk - All GTs, cirrhosis: 12 wk - GT 3 treatment-experienced: 16 wk	- Tablet (FDC) 100/40 mg/d	- 12-17 y: 300/120 mg/d

genotype 4 infection which is the commonest in Egypt. Thus far, the experience with sofosbuvir/ledipasvir in the same age cohort was limited to 34 children enrolled in the industry-driven trial that led to the approval of the use of this combination by the United States Food and Drug Administration (USFDA) and European Medicines Agency (EMA) for children between 3 and 6 years of age.[21] In this trial, only one patient was infected with HCV genotype 4, and the combination of sofosbuvir/ledipasvir was administered for 12 weeks and provided as granules 150/33.75 mg for children weighing <17kg or tablet 200/45 mg for those with a weight ≥17kg. The appropriateness of the doses selected was confirmed by the pharmacokinetic analyses that showed, for both the granules and the tablets, plasma exposures of sofosbuvir and ledipasvir comparable with those observed in the Phase II and III studies conducted in adults. The SVR_{12} was 97% (33/34) and the only patient who did not achieve this virological milestone was a 3-year-old child who discontinued treatment after 5 days of dosing because of "abnormal drug taste".[21] Looking at the details of the two above-described studies it should be noted that swallowing difficulties could apparently impact the compliance with the treatment in such young children.[20,21] As a fact, in the study by Kamal and collaborators a 3-year-old child vomited after the first dose of the drug.[20] The authors advised to grind the tablets in juice in the case of difficulty in swallowing and the patient apparently managed to complete treatment, although this solution, albeit effective in this small pilot study, could affect the absorption of the drugs and potentially impact the effectiveness of treatment in the real life. The absence of pharmacokinetic analysis, both for children swallowing the entire or the grinded tablets, is a major limitation of the study by Kamal and collaborators.[20] In paediatric studies, whenever a new drug formulation is tested in children of different ages or belonging to a specific and different weight band, it is mandatory to evaluate the drug's exposure by characterising absorption, distribution, bioavailability, metabolism and excretion of the drug. This aspect is relevant as the availability of generic drugs in LMICs has been crucial for improving the access to HCV treatment for adults as it will be, in the future, for children. Thus far, three different regimens have been approved by the USFDA and the EMA for use in children and adolescents with age-specific limitations (Table 1): sofosbuvir/ledipasvir, sofosbuvir *plus* ribavirin and glecaprevir/pibrentasvir. While it is reasonable to think that these combinations will soon be available, or in some cases already are, for paediatric use in high-income countries, it is unlikely that the number of children and adolescents with chronic HCV infection living in LMICs will get access to the branded and patented medicines. Voluntary licensing, an agreement between an originator manufacturer and a generic manufacturer that allows the production and sale of a patented drug in certain countries, subject to licensing terms, has been increasingly used to expand access to patented key drugs for HCV infection in adults.[21,26] Voluntary licensing of DAAs has been demonstrated to substantially improve HCV treatment uptake in eligible countries for adults and, in the future, will be more and more relevant for children. Generic drug makers are not required to repeat the clinical trials of new drugs but whenever a new paediatric drug formulation is developed it is important that it undergoes rigorous testing.

In conclusion, the study by Kamal and collaborators confirms that DAA regimens appear to be safe and effective for children with chronic HCV infection as young as 3 years of age. While it is important to include children and adolescents in the ambitious WHO plan in eliminating viral hepatitis as a major public health threat by 2030, a cautious approach is needed with well-designed clinical trials fulfilling the three phases of clinical drug development before the widespread paediatric use of these new drugs.

CONFLICT OF INTEREST

Edoardo G. Giannini: speaking and teaching for AbbVie and Gilead Sciences. Giuseppe Indolfi: principal investigator in Gilead Sciences sponsored trials.

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