Treatment of Hepatitis C Virus Infection in Children: Time for Action

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Abbreviations: IFN, interferon; DAA, direct acting antiviral; CHC, chronic hepatitis C; VR, virological response; HCV, hepatitis C virus; LT, liver transplantation; PR, pegylated IFN and ribavirin; EMA, European Medicines Agency; FDA, Food and Drug Administration.

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Since 2013, eight different DAAs regimens have been approved for use in adults with chronic hepatitis C (CHC) infection (table 1) with excellent efficacy (sustained virological response [SVR] rates >90%) and safety profiles. Patients historically considered difficult to treat in the IFN era, such as adults with human immunodeficiency virus co-infection or with hepatitis C virus (HCV)-related compensated cirrhosis, can now be easily treated y, achieving high VR rates after 12 weeks of treatment (1).

The incidence of graft dysfunction and progression to cirrhosis is higher and the overall survival rate is lower in patients transplanted for CHC when compared to patients with other LT indications, but this can now be prevented by achieving SVR before LT (2).

Despite advances in DAA therapy, treatment of children with CHC has remained based on pegylated-IFN with ribavirin (PR)(3). Although children will typically tolerate the side effects of IFN, its use is a challenge for the patients, their careers, and for the medical team.

It is true that very few children develop end-stage liver disease due to CHC and for most HCV-positive transplanted children the indication for LT is a different underlying condition. Children transplanted *with* HCV (or who contracted HCV from the graft) have a remarkably better outcome than those transplanted *because of* HCV (4). In Italy, a national registry studying the natural course of pediatric HCV over 15 years showed that 6/332 (1.8%) children had developed end-stage liver disease at a median age of 9.6 years (5). In our personal experience, however, HCV infection post-LT had a significant impact on these children.

In this issue of *Liver Transplantation*, Huysentruyt et al. describe two children with HCV infection and cirrhosis successfully treated with ledipasvir/sofosbuvir and ribavirin for 12 weeks (6). The first child, a one-year-old boy with biliary atresia, received treatment perioperatively while the second, a 16-year-old girl with Budd-Chiari syndrome and cirrhosis, was treated post- LT. The study by Huysentruyt et al. raises up the discussion about the development and use of DAAs for children. The time frame from compound discovery to development and registration of the different regimens for adult use has been extraordinary short. This success can be ascribed in part to regulatory

changes. The European Medicines Agency (EMA) and the Food and Drug Administration (FDA) agreed to permit phase two studies of all oral regimens with DAAs without standard-of-care comparators facilitating rapid drug testing and approval. The most recent regimen approved for use in June 2016 for adults with CHC was for sofosbuvir and velpatasvir (7). This 12-weeks schedule is highly effective (sustained VR rates >95%) in all patients, independently of treatment history and of the presence of cirrhosis with pangenotypic (1 to 6) efficacy. Despite these impressive results only four pediatric trials are currently ongoing worldwide (table 1). The three regimens tested in these trials lack the characteristics of the most recent, new-generation treatments approved in adults with approval of these drugs in children still remote.

Only limited preliminary data are available on the use of DAAs in children. Pharmacokinetics of sofosbuvir and ledipasvir/sofosbuvir in HCV-infected children older than 6 years of age have been reported recently (8-9), as well as the safety and efficacy data of in adolescents (10-12). Although the off-label use of drugs should always be discouraged when alternatives are available, in the case of DAAs the excellent results obtained in adults and the very positive preliminary results in pediatric studies (VR rates 97-100%) makes it hard to justify the continued use of PR.

Extrapolation of efficacy from adult studies (an approach previously demonstrated to be effective in IFN-based treatments), preliminary results from pediatric registration trials, and case reports describing the successful off-label use of the regimens, support the hypothesis that these new regimens should be effective and well tolerated in pediatric patients also. Clearly a concerted effort is necessary to extend testing and approval of the most effective DAA regimens in children. Most importantly, the target of global eradication of HCV may be jeopardized if the pediatric reservoir is disregarded.

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Table 1. EMA and FDA-Approved Regimens for Treatment of Chronic Hepatitis C in Adults, and ongoing pediatric studies

Drugs approved in adults	**Genotypes**	**Ongoing Pediatric Studies**		
		ClinicalTrial.gov accession number	*estimated completion date*	*data available*
sofosbuvir + ribavirin	2,3	NCT 02175758	April 2018	PK 6-18 years of age;[8,9] efficacy and safety 12-18 years[11]
sofosbuvir + simeprevir	1,4			
sofosbuvir/ledipasvir (FDC)	1,4-6	NCT 02249182 NCT 02868242	April 2018	PK 6-18 years of age;[8,9] efficacy and safety 12-18 years[10,12]
ombitasvir/paritaprevir/rit (FDC) (± dasabuvir) (FDC)	4, (1)	NCT 02486406	January 2023	none
sofosbuvir + daclatasvir	1-4			
elbasvir/grazoprevir (FDC)	1,4-6			
sofosbuvir/velpatasvir (FDC)	1-6			

Note: FDC, fixed dose combination; PK, pharmacokinetics.