# Treating hepatitis C virus in children: time for a new paradigm

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## Abstract

Hepatitis C virus infection is a leading cause of liver-related morbidity and mortality. In the paediatric population, HCV infection is underdiagnosed and undertreated in the absence of robust screening policies worldwide, and a lack of tolerable, effective treatment. The recent advances in HCV drug development allow for optimism, a change in outcomes for the millions of children infected with this virus and a unique opportunity for strategies aiming at HCV eradication. The rapid development of the new compounds has been followed by a welcome shift in the regulatory processes; however, strategies aiming at improving diagnosis, selecting the best combinations and addressing mother-to-child transmission issues are required for the new therapeutic agents to be introduced safely and effectively in the paediatric population and to contribute to the goal of virus eradication.

Keywords: hepatitis C virus, direct-acting antivirals, paediatric treatment, cure

## Epidemiology of paediatric HCV

There are an estimated 130–150 million people living with chronic hepatitis C virus (HCV) infection worldwide, around 700,000 deaths from HCV-associated causes each year and 3–4 million new infections estimated to occur annually [1,2]. HCV seroprevalence is highest in Central Asia, West and Central sub-Saharan Africa, North Africa/Middle East and Eastern Europe, with Egypt having the world's highest prevalence, at around 15%.

Data are limited regarding the global burden of paediatric HCV infection, with modelled estimates suggesting that there are 11–13 million children living with HCV. Furthermore, a high proportion of children with HCV will not be diagnosed. In a recent study in the US, where HCV prevalence in children is 0.2–0.4%, only one-in-seven children with HCV were identified and less than 2% were offered treatment [3]. Mother-to-child transmission is the leading source of HCV infection in children, although other modes of acquisition may also occur, including nosocomial transmission (e.g. through blood transfusions or unsafe injections) and injecting drug use.

## Natural history of paediatric HCV infection

Chronic infection develops in most HCV-infected children, with around 7–20% experiencing spontaneous viral clearance in European studies [4-6]. Prospective studies have shown that progression of liver fibrosis to cirrhosis is infrequent in children with chronic HCV infection, occurring in around 2–3% [4]; however, there are case reports of children with cirrhosis aged as young as 3 or 4, while rare cases of hepatocellular carcinoma (HCC) in adolescence have been reported [7]. Data from the PEDS-C trial on children with chronic HCV demonstrate that fibrosis is progressing during childhood: among the 44 children with repeated liver biopsies, on average 6 years apart, nearly one-third showed an increase in severity of fibrosis and the proportion of patients with bridging fibrosis/cirrhosis nearly doubled, increasing from 11% to 20% [8]. Groups at increased risk of more rapid disease progression include children with thalassaemia major, where hepatic iron overload contributes to fibrosis progression [9], children with HIV co-infection [10] and childhood cancer survivors [6].

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Although few children will experience end-stage liver disease during childhood, they will be at risk of cirrhosis and HCC in early adulthood given that liver fibrosis development directly correlates with increasing age and duration of infection [11]. In a study of adults with HCV, a 26-fold increased risk of liver-related death associated with childhood-acquired HCV was reported [12]. Extrahepatic manifestations of chronic HCV infection in adults include renal insufficiency, diabetes and insulin resistance, B-cell lymphoproliferative diseases, cardiovascular disease and neurocognitive manifestations, particularly fatigue and depression [13]. Although development of non-organ-specific autoantibodies and subclinical hypothyroidism are common, and present in young children [14], there is limited knowledge of the medium- to long-term impact of HCV-related inflammation on extrahepatic manifestations in children. Other aspects of living with chronic HCV include the fact that the infection can be considered a stigmatised health condition, which can impact on quality of life.

## Benefits of cure: adult data

In the pre-direct-acting antiviral (DAA) era, sustained virological response (SVR) 24 (i.e. sustained loss of serum HCV RNA for 6 months following treatment end) was found to be a good predictor of 'cure' [15]. Clear evidence of the clinical benefits of HCV cure with respect to long-term outcomes in adults was provided in a recent meta-analysis of 35,000 adults: among HCV-monoinfected, non-cirrhotic cohorts, SVR resulting from treatment with interferon/ribavirin (IFN/RBV) regimens was associated with a 62%-decreased risk of all-cause mortality compared with those without SVR, with this being 84% in cirrhotic cohorts and 73% in those with HIV co-infection [16]. Eradication of HCV reduces risk of adverse clinical outcomes even for patients with no or minimal liver fibrosis.

## Direct-acting antivirals

The development of DAAs has been a turning point in the therapeutic management of chronic HCV infection, with extraordinary advances with respect to compound discovery, development and registration in a very short time frame. Adult clinical trials of new DAA regimens have reported SVR rates above 95% with treatment durations of ≤12 weeks in a range of patient groups including those for whom prior treatment has failed, those with cirrhosis and those with HIV co-infection [17]. Phase III trials of new DAA regimens have reported low rates of

severe adverse events, but with higher toxicity associated with ribavirin-containing regimens [17]. There is a robust HCV treatment pipeline, with all-oral, fixed-dose combination regimens in development that are interferon- and ribavirin-free and with pan-genotypic activity.

## Treating children and paediatric development of DAAs

Despite new DAAs for adults having been available for some time (sofosbuvir was approved in 2013), there has been significant delay in evaluating their use in treating children with chronic HCV infection and DAAs are not yet licensed for paediatric use. Current standard of care for treatment of children therefore remains pegylated (peg)-IFN/RBV regimens, which have well-known toxicities (including growth deficits that are unique for children), inconvenient administration route via subcutaneous IFN injections, poor efficacy and require long durations of treatment. A meta-analysis of eight trials demonstrated that treatment with peg-IFN/RBV results in SVR in 58% of children after 6–12 months of treatment, ranging from 52% with genotype 1 or 4 and 89% with genotype 2 or 3 [18]. There are limited long-term studies of successfully treated children, but these have shown durability of SVR, consistent with findings from adult studies: in a follow-up study of 97 children treated with IFN-$\alpha$-2b/RBV (of whom 56 achieved SVR), the probability of maintaining SVR at 5 years was 98% [19].

Guidelines of the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition recommend IFN/RBV treatment should be considered for children with persistently elevated liver enzymes and/or evidence of liver fibrosis [20]. The rationale for treatment in childhood is prevention of HCV-associated liver damage and extrahepatic disease; viral eradication also means that a child can live free of a socially stigmatising infection. To date in Europe, only a minority of children with chronic HCV have been treated. This partly reflects the limitations of peg-IFN/RBV therapies for children, but also the 'watchful waiting' approach of some paediatric hepatologists with respect to starting peg-IFN/RBV treatment, particularly for 'harder-to-treat' genotypes (e.g. genotypes 1 and 4) The availability of IFN-free, highly potent new compounds for future paediatric use will undoubtedly reframe the debate regarding indications for treatment of HCV in childhood. In the likely event of DAAs being shown to be safe and effective in children, the foremost rationale for treating children will shift to viral eradication. On the basis of adult clinical trials of DAA regimens, there is potential to cure paediatric HCV in the vast majority of children treated.

Paediatric Investigation Plans (PIPs), which are mandatory developmental plans to support the authorisation of a medicine for children, have been submitted by pharmaceutical companies to the European Medicines Agency (EMA) for several combination DAA regimens or drugs for use in combination. There are currently almost 20 PIPs on DAAs agreed by the EMA's Paediatric Committee and, reflecting the substantial treatment pipeline, many others will follow. Although paediatric studies for telaprevir and boceprevir (first generation antivirals used with peg-IFN/RBV, now discontinued) were initiated, these were postponed due to lack of recruitment. This reflected the poor side-effect profile of these drugs in adults, the lack of immediate urgency for treatment in the paediatric context and, critically, the prospect of new, more effective, better tolerated and less toxic regimens in the near future. Paediatric trials of some DAA regimens (e.g. sofosbuvir/ledipasvir fixed-dose combination [ClinicalTrials.gov Identifier: NCT02249182] and sofosbuvir+ribavirin in adolescents and children with genotype 2 or 3 [ClinicalTrials.gov Identifier: NCT02175758]) have now started. However, the current timelines for completion of approved PIPs for DAA regimens are far off, for example 2020 for grazoprevir/elbasvir; 2022 for simeprevir; and 2023 for daclatasvir/asunaprevir/beclabuvir.

## EMA's new approach to paediatric registration of DAAs

Challenges to starting and conducting paediatric trials for DAA regimens include the growing number of compounds at different stages of approval, current regulatory requirements for drug registration, the need to identify the target population for treatment and the relatively small number of diagnosed children with chronic hepatitis C available for recruitment into clinical studies. There is also currently no possibility for a PIP to be submitted incorporating a combination of drugs across companies. This acts as a further barrier to achieving rapid registration of the best combination for treating children with HCV infection.

Key issues to be addressed within a regulatory framework include prioritisation of DAA regimens for paediatric development, the strategy for extrapolating data from adult clinical trials and determining what criteria should be applied in selecting the most promising regimens for treating children. In December 2014, an expert meeting on paediatric development of hepatitis C drugs was held to address these issues 'in order to agree with applicants' high-quality and feasible Paediatric Investigation Plans (PIPs) for hepatitis C therapy that will ensure rapid access of children to these innovative new therapies' (www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2014/12/event_detail_001074.jsp&mid=WC0b01ac058004d5c3). The key findings of this meeting are summarised in Table 1.

This updated strategic approach to the registration of DAA regimens for paediatric use, particularly the fact that regimens can now be approved on the basis of Phase I/II clinical studies of 30–40 children, should help to accelerate paediatric access to treatment. It is expected that pharmaceutical companies with PIPs already agreed by the EMA will apply to modify these in order to align with this new regulatory approach. Post-authorisation safety and efficacy studies will be essential to ensure the safe and effective use of new regimens and to build the necessary evidence-base to facilitate healthcare decisions.

## Accelerating paediatric HCV research in the DAA era

The new therapeutic context is likely to catalyse research efforts to address some of the important gaps in current knowledge of the epidemiology and natural history of chronic HCV infection acquired vertically or in childhood. These include the longer-term clinical outcomes of chronic HCV acquired vertically or in childhood and the extent of undiagnosed paediatric HCV infection. A fuller understanding of the disease course in children and adolescents with chronic HCV, together with registration of new regimens for paediatric use, will allow the design of future strategy trials to address how best to treat and care for children and adolescents with chronic HCV infection in the DAA era. For example, there is an expectation, partly based on peg-IFN/RBV treatment responses being higher in children than in adults, that it might be feasible to treat children with DAA regimens for shorter periods than adults (Table 1). Other important clinical management questions include identifying the best combinations

**Table 1.** Expert opinion on how paediatric clinical studies on DAAs should be conducted, EMA Expert meeting on the clinical investigation of medicines for the treatment of paediatric hepatitis C (www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2014/12/event_detail_001074.jsp&mid=WC0b01ac058004d5c3)

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| *Drug prioritisation for paediatric development* |
| ◆ Feasibility of conducting all current PIPs is questionable |
| ◆ Limited number of patients may result in a scenario where only the earliest PIPs will produce results, but these may not involve best regimens for children |
| ◆ Prioritisation of some regimens for paediatric development would be useful in principle. Factors to consider for prioritisation:<br>❖ Acceptable safety profile<br>❖ Tolerability<br>❖ Efficacy in adult trials with SVR12 >90–95%<br>❖ Palatability and age-appropriate formulations (can be required by PDCO in a PIP) |
| ◆ Longer deferral for PIP timelines for first generation DAAs that are no longer of key interest for children, to enable potential application for future waivers |
| *Clinical trial design and feasibility issues* |
| ◆ IFN/RBV-experienced children should be included in trials, but there should be no requirement to specify minimum numbers; future trials should include children whose DAA regimens have failed |
| ◆ Given expected high efficacy of the multiple DAA regimens approved in adults and in development, comparative trials seem unrealistic and may be unnecessary |
| ◆ Genotype coverage of paediatric clinical trials should reflect that of adult trials |
| ◆ Whether treatment duration can be shorter for children than for adults should be investigated, as children are expected to have better SVR rates than adults |
| ◆ Response-guided therapy unlikely to be feasible or needed |
| ◆ Consensus that long-term follow-up of trial participants with SVR should be 2–3 years |
| ◆ Pre-authorisation studies could be limited to 30–40 participants<br>❖ Pharmacokinetics<br>❖ Limited tolerability and efficacy data |
| ◆ Post-authorisation safety and efficacy studies to follow licensing of regimens, to collect longer-term and more detailed data |

EMA: European Medicines Agency; DAA: direct-acting antiviral; PIP: Paediatric Investigation Plans; PDCO: Paediatric Committee; IFN-RBV: interferon-ribavirin

for treating children, determining when to initiate treatment, and how to manage the (likely to be small) group of children who fail to achieve SVR. Key groups at increased risk of worse outcomes, such as children with evidence of fibrosis, thalassaemia, HIV or HBV, may be prioritised for treatment. There will also be a need to conduct robust health technology assessments on treating children with DAAs, to incorporate cost-effectiveness, acceptability and quality of life.

## Conclusions

It is important that innovations in HCV treatment reach children as quickly as possible, in order to allow discontinuation of the use of less effective and more toxic interferon-based therapies. The EMA's new strategy should enable a more timely registration of DAA regimens for paediatric use within Europe, which in turn will enable the key questions around optimal paediatric management to be addressed. It remains to be seen whether the US Food and Drug Administration will adopt a similar approach. As there is now potential to cure paediatric HCV, the vision should be to aim for an HCV-free generation of children in the near future.

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