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New Prospects for the Treatment and Prevention of Hepatitis C in Children

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Abstract

Purpose of review—Combined pegylated interferon- α and ribavirin remain the standard therapy for pediatric hepatitis C virus (HCV) infection in 2016, but direct acting antivirals (DAAs) with greatly improved efficacy and safety are now approved for adults. Here we review the major classes of DAAs and their anticipated use for treatment and potentially prevention of HCV in children.

Recent findings—Currently approved DAAs target the viral protease, polymerase, and NS5A, a protein involved in viral replication and assembly. In combination, they have lifted sustained virologic response rates to over 90% for multiple HCV genotypes, and the rich DAA pipeline promises further improvements. Clinical trials of interferon-free DAA regimens have been initiated for children ages 3–17 years. The first efficacy trial of a preventative HCV vaccine for adults is also underway. While awaiting a vaccine, there is hope that increased DAA uptake may prevent pediatric HCV infections by shrinking the pool of infectious persons.

Summary—Interferon-free DAA regimens have revolutionized therapy for HCV-infected adults and pending results of pediatric trials will likely do the same for HCV-infected children. If widely deployed, particularly amongst individuals likely to transmit HCV, DAA therapies may also help reduce new vertically- and horizontally-acquired pediatric infections.

Keywords

Hepatitis C virus; direct acting antiviral; therapy; pediatrics; vertical transmission

Introduction

The hepatitis C virus (HCV) remains a major cause of liver disease more than a quarter century since its discovery. An estimated 115–185 million individuals have serologic

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evidence of HCV infection, including roughly 11 million children under the age of 15 years [1, 2]. Vertical transmission, injection drug use (IDU), and iatrogenic exposures account for most pediatric infections. While some of these infections resolve spontaneously, approximately 60–80% of vertically- and horizontally-acquired pediatric HCV infections persist indefinitely [3–5]. Persistent hepatitis C infections predispose to complications including hepatic fibrosis, cirrhosis, and hepatocellular carcinoma. Of individuals who acquire HCV as adults, approximately 10–20% develop cirrhosis after 20–30 years of infection, with a subsequent 3–6% annual risk of hepatic decompensation and 1–5% annual risk of hepatocellular carcinoma [6]. Liver disease progresses more slowly in children, with only 1–2% of those infected as infants developing cirrhosis during childhood [7, 8]. Nevertheless, most children who undergo liver biopsy demonstrate some degree of liver inflammation, often with mild fibrosis, and there remains concern that without treatment a significant proportion of HCV-infected children could go on to develop advanced liver disease over their lifetime [9–11].

Pediatric HCV therapy in 2016

Successful treatment of HCV can halt progression of liver disease and prevent transmission to others, but in 2016 most HCV-infected children are not treated. An obvious reason is that most pediatric HCV infections are not diagnosed; by one estimate only 5–15% of HCV-infected children in the U.S. are identified [12]. Secondly, limitations of approved therapies coupled with the mild course of pediatric HCV result in deferral of therapy for many children with known HCV infection. The standard therapy for HCV-infected children aged 3–17 years is combination pegylated interferon-alpha (pegIFN α) and ribavirin (RBV) [3]. For genotype (GT) 1, the most prevalent HCV genotype in the U.S. and globally [2], 48 weeks of therapy results in a sustained virologic response (SVR) in less than 50% of children [13]. GT2 and GT3 infections are more responsive to pegIFN α /RBV therapy, with SVR rates approaching 90% in pediatric trials [13, 14]. Although children tolerate this regimen better than adults, a substantial proportion still experience side effects including influenza-like symptoms, leukopenia, and anemia. Beyond this, interferon-based therapies transiently impair vertical growth [13, 14]. Given the slow pace of liver disease in most HCV-infected children, suboptimal efficacy and substantial toxicity of pegIFN α /RBV, and stunning performance of new all-oral interferon-free direct acting antiviral (DAA) regimens in adults, many persistently infected children are being “warehoused” until they too have access to all-oral DAA therapies [15]. However, standard treatment without delay may be advised in the rare instance of rapidly progressive pediatric liver disease, particularly when caused by the more interferon-responsive genotypes 2 and 3 [3, 15].

Origins of the DAA revolution

Drug discovery efforts for HCV were hampered for years by inability to culture the virus in cell culture. Eventual development of a subgenomic replicon system in 1999 [16] and a pseudoparticle system in 2003 [17] facilitated studies of HCV intracellular replication and viral entry. Another major breakthrough came in 2005 with discovery of a genotype 2 virus capable of replicating in a permissive hepatoma cell line [18]. Using these systems as well as insights gained from resolution of the three dimensional structures of several HCV

proteins, antivirals have been developed by rational drug design and compound screening [19, 20]. Experimental targets of anti-HCV therapies now include the envelope glycoproteins E1 and E2, non-structural viral proteins NS3, NS5A, and NS5B, and host factors affecting the viral entry and replication including scavenger receptor B1 (SRB1), CD81, cyclophilin A, and miR122 (Figure 1) [19, 21, 22]. This review will focus on inhibitors of the viral NS3/4A protease, NS5A, and the NS5B polymerase, drug classes that are already approved for use in adults and most likely to enter clinical care for children in the near term.

NS3/4A protease inhibitors

The first DAAs to enter clinical practice targeted the HCV NS3/4A protease. This heterodimeric serine protease cleaves 4 sites along the viral polyprotein to release individual HCV proteins [20, 23]; it also cleaves several adaptor proteins in innate immune signaling pathways to counter host antiviral defenses [24, 25]. Compounds that bind the protease catalytic site potentially reduce HCV replication. First generation protease inhibitors telaprevir and boceprevir were approved in 2011 for use in combination with pegIFN α /RBV to treat adults chronically infected with HCV GT1. Addition of either one of these drugs boosted SVR rates in treatment-naïve individuals from 40–44% to 67–75% [26, 27] and also benefitted treatment-experienced populations [19, 28].

Despite being a significant milestone in the evolution of HCV therapy, the advent of “triple therapy” combining protease inhibitors and pegIFN α /RBV left much room for improvement. SVR rates were still less than desired, particularly in populations such as prior null-responders to pegIFN α /RBV [19]. Telaprevir and boceprevir also added significant toxicity to an already difficult regimen, including rash in the case of telaprevir and exacerbations of ribavirin-induced anemia with both [19]. The drugs also had a low genetic barrier to resistance; any of a number of single nucleotide point mutations could render viruses resistant [29]. Substantial diversity of the viral protease across genotypes meant that the drugs had limited cross-genotypic activity. Finally, frequent drug-drug interactions presented challenges [23]. Studies of both telaprevir and boceprevir were initiated in children (and completed in the case of telaprevir), but neither drug is expected to be a component of future pediatric HCV care given the rapid development of safer and more effective alternatives (NCT01701063 and NCT01425190; www.clinicaltrials.gov).

NS3/4A inhibitors are still expected to be important components of future DAA regimens. After telaprevir and boceprevir, the so-called “first-generation, second-wave” protease inhibitors simeprevir and paritaprevir were approved in 2013 and 2014, demonstrating improved efficacy and less toxicity. Second generation protease inhibitors that boast pan-genotype activity and higher barriers to resistance have now reached phase III clinical trials. A summary of protease inhibitors that are now approved or in advanced clinical trials can be found in Table I.

NS5A inhibitors

NS5A is a non-enzymatic protein that participates in the formation of the HCV replicase complex and in viral particle assembly. NS5A inhibitors block both functions and are among

the most potent DAA for HCV [26]. Approved NS5A inhibitors have broad cross-genotypic activity, with daclatasvir classified as pan-genotypic. The NS5A protein lacks a human homolog, and its inhibitors are well tolerated [26]. An important downside of this class is its low barrier to resistance. Moreover, many NS5A resistant variants replicate efficiently and can persist for long periods in individuals after treatment failure [30]. Currently approved first generation NS5A inhibitors include daclatasvir, ledipasvir, and ombitasvir, and second generation DAAs are in development (Table 1).

NS5B polymerase inhibitors

The NS5B protein functions as the RNA-dependent RNA polymerase for HCV and has been a major focus of drug development efforts. Inhibitors of NS5B fall into one of two classes: nucleos(t)ide polymerase inhibitors (NPI) and non-nucleos(t)ide polymerase inhibitors (NNPI).

NPI are nucleoside or nucleotide analogues that are incorporated into the emerging RNA strand by the NS5B polymerase, preventing incorporation of additional nucleotides. NPI demonstrate broad cross-genotypic activity due to the highly conserved nature of the NS5B active site. Although single amino acid substitutions confer resistance to NPI, emergence of resistant variants is rare because these variants tend to exhibit significantly impaired viral replicative fitness without additional compensatory mutations [31]. NPI are delivered as pro-drugs requiring hepatic conversion to limit systemic exposure. Toxicity has nevertheless halted the development of numerous NPI, in some cases thought related to off-target effects on mitochondrial RNA polymerases [31]. At present the only NPI approved for treatment of chronic HCV infection is sofosbuvir, a well-tolerated and potent nucleotide NS5B inhibitor with nearly pan-genotypic activity. Sofosbuvir was a component of the first all-oral DAA regimens for HCV and has entered pediatric trials (NCT02175758, NCT02249182).

The NNPI class comprises diverse antivirals that bind any one of five non-catalytic sites on NS5B, limiting its ability to undergo the conformational changes needed for polymerase activity [31]. As a group they tend to have low barriers to resistance and narrow genotypic activity [28]. One NNPI that binds a domain in the polymerase “palm”, dasabuvir, has been approved as a part of a four drug cocktail for GT1, and several other NNPI are in advanced clinical trials (Table 1).

Combating HCV with DAA cocktails

Combining multiple classes of HCV antivirals, as in HIV therapy, raises the overall barrier to resistance and substantially improves SVR rates. 2013 saw the first approval of an all-oral (interferon-free) combination regimen for HCV: the polymerase inhibitor sofosbuvir with RBV for GT 2/3 infections. That same year the protease inhibitor simeprevir was approved, and in combination with sofosbuvir provided an all-oral DAA option for GT1. Twelve to 24 week courses of these regimens resulted in SVR rates of 90% or higher for certain populations [32, 33]. In 2014, the FDA approved the first fixed-dose single tablet DAA regimen of sofosbuvir with the NS5A inhibitor ledipasvir for GT1, boosting SVR rates to over 95% even in individuals with prior treatment experience [34, 35]. Just months later, the all-oral NS5A, protease, and polymerase inhibitor cocktail of ombitasvir + paritaprevir/

ritonavir + dasabuvir +/- ribavirin offered another highly effective regimen for GT1 [36]. These DAA regimens also provide options for GT4-6 viruses.

In the interferon era, HCV GT3 viruses were considered among the easier genotypes to treat [13], but in the DAA era SVR rates for GT3 are comparably low, particularly in treatment-experienced patients with cirrhosis [37]. The recently available pan-genotypic NS5A inhibitor daclatasvir, when used in combination with sofosbuvir, now offers an interferon-free DAA options with improved SVR rates for GT3 [38]. To improve activity in difficult-to-treat populations, mitigate the threat of multidrug HCV resistance, and further simplify HCV treatment, future DAA cocktails will likely combine DAAs from multiple classes that each have pan-genotypic activity and higher barriers to resistance. Given the rapidity of DAA development, “living documents” such as the IDSA/AASLD guidelines (www.hcvguidelines.org) that keep pace with newly approved regimens for all HCV genotypes are vital for helping clinicians select therapies for their patients.

Prospects for bringing DAAs to children

As of 2016, phase II/III trials of combination DAAs for children ages 3–17 years chronically infected with GT 1, 2, 3, and 4 are underway, as listed in Table 2. If found to be as safe and effective in children as they are in adults, these regimens will almost assuredly replace interferon-based regimens and significantly alter the approach to treatment of pediatric HCV. Rather than deferring therapy until a particular age or waiting for evidence of significant liver disease, treatment could be given as soon as a diagnosis of chronic hepatitis C were made. That being said, in cases of vertical transmission there may be rationale to defer therapy until age 3 years due to the relatively prolonged capacity of infants and toddlers to spontaneously resolve infection [5, 13].

One potential obstacle to rapid widespread dissemination of DAA therapies for children is their high cost, a factor which has already resulted in rationing of DAA therapies for adults to those with advanced liver disease [30]. There is hope that costs will fall due to increasing competition if not public pressure. How pediatric HCV regimens will be priced and how insurance companies will prioritize chronically infected children who have a lifetime of risk if not treated remains to be seen.

A second impediment to delivery of DAA therapies to HCV-infected children is the reality that the vast majority of pediatric HCV infections remain undiagnosed [12]. Improved identification of vertically-infected children will require both better detection of HCV-infected pregnant women [39], possibly through implementation of universal antenatal screening in some locales [40], and more comprehensive efforts to ensure that vertically-exposed infants receive proper testing. Strategic use of electronic medical record systems to track HCV-exposed infants and inclusion of early HCV-RNA PCR (such as at age 2 months) in the testing schema may be means to reduce the number of children who are lost to follow-up without any HCV testing [41]. Increased screening of adolescents with a history of IDU is also needed to ensure that more horizontally-acquired cases are identified. One can hope that imminent availability of highly effective, well-tolerated DAA regimens to

cure pediatric HCV infections may provide the impetus to boost public health efforts to identify HCV-infected children.

New prospects to prevent HCV in children

The major routes by which children acquire HCV include vertical transmission, injection drug use, and iatrogenic transmission. Current prevention efforts center on avoiding exposure to the virus. Obstetric interventions such as cesarean section do not appear to prevent vertical transmission [42], though avoidance of invasive fetal monitoring in labor is advised based on associations of its use with increased transmission in observational studies [42]. Drug treatment programs are important for limiting horizontal HCV transmission by IDU, but have failed to curtail a rapid increase in new cases of IDU-related HCV among adolescents in the past decade in the U.S [43]. Standard infection control practices for blood-borne pathogens have largely eliminated iatrogenic acquisition of pediatric HCV in developed nations and have reduced rates in many resource limited-countries, but ongoing iatrogenic transmission remains problematic in numerous endemic regions [44].

Interestingly, DAA therapies may offer a powerful new tool to prevent pediatric HCV infections. Widespread distribution of potent and well-tolerated regimens could prevent new HCV infections by reducing the pool of infectious individuals. Nevertheless, several challenges face this “treatment-as-prevention” approach, including the need to convince payers and providers to offer very costly treatment to individuals most likely to transmit the infection (and most susceptible to re-infection) such as active IDU [45]. In endemic nations with infection control lapses that allow ongoing iatrogenic transmission of HCV, major funding and infrastructure issues must be addressed to identify and treat sufficient numbers of HCV-infected individuals to reduce the incidence of new infections [19, 46].

With their improved safety profile, DAAs may be particularly suited for preventing pediatric HCV acquired by vertical transmission. Important regimens including sofosbuvir + ledipasvir and ombitasvir + paritaprevir/ritonavir + dasabuvir appear safe in animal reproduction studies and have earned FDA category B ratings in pregnancy, a marked contrast from the teratogenic properties of ribavirin (category X) that precluded use of pegIFN α /RBV in women during and 6 months prior to pregnancy [47]. These favorable pregnancy safety ratings for DAAs have raised interest in using them to treat pregnant women to prevent vertical transmission [7], analogous to use of antiretroviral therapy to prevent perinatal HIV transmission. However, these regimens have not yet been tested in human pregnancies, and important distinctions between HCV and HIV warrant consideration. Besides the lower transmission rate for HCV [48], vertically acquired HCV is not imminently dangerous for infected children and will likely be easily curable with DAAs. Thus the “reward” for preventing HCV vertical transmission is significantly less than the reward for preventing HIV and arguably HBV vertical transmission. Large studies confirming safety and efficacy of DAAs in pregnancy will be necessary to justify their use in pregnancy over identifying and treating the 5% of children who acquire HCV from their mothers [3, 48]. One approach would be to test DAAs in pregnant women at highest risk of transmitting HCV to their offspring. Higher levels of viremia have generally been associated with a greater risk of transmission, but considerable overlap exists between viral loads of

transmitting and non-transmitting mothers [49]. Maternal HIV co-infection was previously linked to a 2–4 fold increased risk of HCV vertical transmission [48], but recent evidence suggests that HIV co-infected mothers who are well controlled on highly-active antiretroviral therapy may be no more likely to transmit HCV than HIV-negative mothers [50, 51]. Thus, more work is needed to clarify which women are at the greatest risk of transmitting HCV and potential candidates for interventional trials to limit HCV vertical transmission [23]. An ongoing large trial by the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network may prove useful in this regard. While the potential role of DAA therapy in pregnancy remains to be determined, an alternative prevention approach that is already available is to provide DAA treatment to HCV-infected women of childbearing age who wish to get pregnant in the future. This approach both cures maternal infection and prevents future vertical transmission events and is already advocated in current HCV treatment guidelines (www.hcvguidelines.org).

Finally, it is important to note that the first ever efficacy trial of a preventative HCV vaccine is currently underway, testing the ability of a T-cell based vaccine approach [52] to promote resolution of acute HCV infections in adults who inject drugs (NCT01436357). This vaccine, if successful, may first be utilized in select populations such as health care workers, uninfected IDU, or IDU who have been cured of HCV [53], before expansion to broader at-risk populations [46]. It is not clear how an HCV vaccine would be applied to children or whether it could prevent vertical transmission of HCV. The protective effect of newborn vaccination might be limited given that at least one-third of HCV vertical transmission events appear to occur in utero rather than peripartum [54]. Further, the HCV vaccine currently in clinical trials employs replication-defective chimpanzee adenovirus and vaccinia vectors that have not yet appeared to have been vetted for use in newborn humans [52]. The relatively low rate of vertical transmission and potential to use DAA therapies to prevent or manage vertical transmission could limit initial enthusiasm for a trial of HCV vaccination in newborns. Nevertheless, a comprehensive prevention strategy coupling broad immunization of children at risk for HCV with the DAA “treatment-as-prevention” approach will likely be required to achieve the ultimate goal of eliminating hepatitis C [46].

Conclusion

Though liver disease typically progresses slowly in HCV-infected children, treatment is warranted to avert the risk of advanced liver disease and prevent transmission to others. Combined pegylated interferon- α /ribavirin remains the best approved therapy for pediatric HCV in 2016 but has significant toxicity and fails to cure almost half of children infected with the most prevalent genotype. Advances in drug development have recently provided a host of highly effective antivirals targeting multiple steps in the HCV life cycle. Several well-tolerated combinations of DAAs are now approved for use in adults and have entered clinical trials for children. The first pediatric all-oral DAA trial may be completed as early as 2017 (NCT02249182). Families and providers caring for HCV-infected children anxiously await results of these studies and the opportunity to offer better therapies to children. Potent DAA therapies may also prove useful for preventing pediatric HCV infections if provided to women of child-bearing age and other individuals likely to transmit the virus to children. Realization of the ultimate goal to eliminate pediatric HCV locally and

globally will likely require both enhanced efforts to identify HCV-infected individuals for DAA therapy and broad use of an effective HCV vaccine.

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Abbreviations

DAA	direct acting antiviral
GT	genotype
HCV	hepatitis C virus
IDU	injection drug use
NNPI	non-nucleotide polymerase inhibitors
NS	non-structural
NPI	nucleotide polymerase inhibitors
pegIFNα	pegylated interferon-alpha
RBV	ribavirin
SVR	sustained virologic response

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Key points

- Pediatric HCV infection remains a major global health threat.
- Combinations of potent and well-tolerated DAAs targeting the HCV protease, polymerase, and NS5A are now preferred for treatment of HCV in adults and have entered clinical trials in children.
- If proven safe and effective in pediatric trials, DAAs will likely replace interferon-based therapies for HCV-infected children.
- Strategic use of DAAs could eventually help reduce new pediatric HCV infections.

Figure 1.

A schematic of the HCV polyprotein and targets of antiviral therapies. The positive-stranded RNA genome of HCV encodes a single polyprotein approximately 3000 amino acids in length that is cleaved by host and viral proteases into 10 individual proteins. Each of these proteins is essential for the viral life cycle and a potential therapeutic target. Currently approved direct acting antivirals (asterisks) target the viral NS3/4A protease, NS5A, and the NS5B polymerase proteins. Compounds directed at host factors (*italics*) critical for viral replication such as miR122, cyclophilin A, and viral receptors CD81 and SRB1 have also shown therapeutic potential.

Table 1

Characteristics of direct-acting antiviral drug classes approved for use in HCV-infected adults

Characteristics	Protease inhibitors	NS5A inhibitors	NS5B nucleoside inhibitors (NPI)	NS5B non-nucleoside inhibitors (NNPI)
Potency	High	High	High	Variable
Cross-genotype activity	Limited	Broad	Broad	Variable
Barrier to resistance	Low	Low; prolonged persistence of resistant variants	High; resistant variants replicate poorly	Low
DAA's approved* or in phase 2 or 3 clinical trials	Telaprevir* Boceprevir* Simeprevir* Paritaprevir* Asunaprevir Sovaprevir Vaniprevir Grazoprevir ABT-493 GS-9857	Ledipasvir* Ombitasvir* Daclatasvir* Elbasvir Velpatasvir Ravidasvir Samatasvir Odalasvir ABT-530 MK-8408	Sofosbuvir* MK-3682	Dasabuvir* Beclabuvir GS-9669

Table 2

Clinical trials of DAAs in HCV-infected children ages 3–17 years

Clinicaltrials.gov	Sponsor	Phase	HCV genotype and agents	Status
NCT01701063	Vertex, Janssen	1,2	GT1: telaprevir + Peginterferon alfa-2b + ribavirin	Completed
NCT01425190	Merck	1	GT1: boceprevir	Terminated early
NCT01590225	Merck	3	GT1: boceprevir + Peginterferon alpha-2b + ribavirin	Withdrawn prior to enrollment
NCT02486406	Abbvie	3	GT1: ombitasvir + paritaprevir/ritonavir + dasabuvir +/- ribavirin GT4: ombitasvir + paritaprevir/ritonavir + ribavirin	Recruiting
NCT02249182	Gilead	2	GT1 & 4: ledipasvir + sofosbuvir GT3: ledipasvir + sofosbuvir + ribavirin	Recruiting
NCT02175758	Gilead	2	GT2 & 3: sofosbuvir + ribavirin	Recruiting