ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Hepatitis C Virus Infection in Children

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G&H What is the prevalence of hepatitis C virus infection in children?

KM In comparison to adults, the prevalence of this disease is relatively low in children. The overall prevalence of hepatitis C virus (HCV) antibody positivity is approximately 1% to 1.5% in North American children. Looking at specific age groups, approximately 0.2% of children age 6 to 11 years and approximately 0.4% of children age 12 to 19 years are HCV antibody–positive, which equates to approximately 31,000 and 100,000 children, respectively. The prevalence of HCV infection in North America is approximately 0.1% to 2% of all children, with approximately 1.3% of children over the age of 6 years infected; between 23,000 and 46,000 children are infected in the United States and approximately 6,600 in Canada.

G&H What are the most common causes of HCV infection in children?

KM Although vertical transmission of HCV (ie, transmission from an infected mother to an infant) only occurs in approximately 5% of pregnancies in which the mother is HCV RNA–positive, most children with HCV have acquired the infection this way (approximately 60%). The remainder of infections are caused by contaminated blood products, horizontal transmission, and, depending upon the age, transmission via contaminated drug paraphernalia.

G&H Can mother-to-child transmission be prevented or reduced?

KM At this point, universal screening of pregnant women for HCV infection is not recommended unless the subject is identified as having a high-risk history for the infection (eg, intravenous drug use). However, if the subject is found to be infected, treatment is not recommended during pregnancy. Current guidelines for HCV management do not discriminate between methods of delivery, and the decision to deliver by Caesarean section vs vaginal delivery does not depend upon the patient's infected status.

> The pediatric community feels very strongly that treatment should not be held until a child develops advanced liver disease ...

G&H How does the HCV disease course compare between children and adults?

KM Although it is difficult to directly compare due to differing confounding variables, it is generally thought that children fare better than adults for the same duration of infection. The rate of cirrhosis in published pediatric populations with HCV infection is around 2%, but ranges from no cirrhosis to 8%. Bridging (ie, significant)

fibrosis, on the other hand, ranges from 4% to as high as 44% in some series of HCV-infected children. The hepatic inflammation observed with pediatric HCV, in comparison to that observed in adults, is less and generally mild.

G&H When is the appropriate time to initiate treatment in HCV-infected children?

KM Currently, the most effective approved treatment for children is pegylated interferon, α2a or α2b, plus ribavirin. Pegylated interferon α2b plus ribavirin was approved in 2008, while pegylated interferon α2a plus ribavirin was approved in 2011 for children over 3 and 5 years, respectively. Because these treatment regimens have toxicities, it is important to consider the safety and tolerance of the drugs, as well as the likelihood of adherence to therapy and the required monitoring. The pediatric community feels very strongly that treatment should not be held until a child develops advanced liver disease; any opportunity should be taken to intervene earlier and potentially clear the infection and halt the progression of disease before there is significant impact on the patient's health and quality of life.

> ... the metabolism of children may be different from that of adults, and drug effects may be further influenced by weight, area of distribution, or surface area differences.

With the new direct-acting antiviral agents for HCV now approved for adult use (and in clinical trials for pediatric use), the efficacy and tolerance are so excellent, and treatment duration so short, that there may be no medical reason not to treat children with HCV infection if and when these agents are found safe and approved for use in children.

G&H According to the long-term data currently available, how effective is pegylated interferon plus ribavirin for the treatment of HCV infection in children?

KM A number of series have looked at the efficacy of pegylated interferon α2a or α2b plus ribavirin. In children infected with HCV genotype 1 or 4, which tend to be the hardest genotypes to treat with these medications, sustained virologic response (the rate of undetectable virus by polymerase chain reaction 6 months after the end of treatment) is approximately 50% (ranging from 44% to 57% in reported trials). In children infected with HCV genotype 2 or 3, sustained virologic response is typically between 80% and 90%, with several studies showing 100% sustained virologic response.

G&H Are there any significant adverse events or tolerance issues associated with this treatment in HCV-infected children?

KM Much like adults, the most common adverse events are flulike symptoms, and these affect most treated children. Approximately 27% of children who are treated develop neutropenia to the point of requiring a dose adjustment, with a small percentage developing thrombocytopenia or anemia. The adverse events unique to children treated with pegylated interferon are the drug's effects on growth. Most children treated with pegylated interferon and ribavirin will experience decrements in their height, weight, and body mass index (BMI) during treatment that correlate with the duration of treatment. Weight and BMI tend to return to baseline by approximately 48 weeks posttreatment; however, 33% of children experience a significant decrement in height (≥-0.5 *z* score), and for most, this had not returned to baseline 96 weeks posttreatment. The impact on linear growth and its subsequent return to baseline after the end of treatment are most prominent in children younger than age 12 years.

G&H How are patients who do not respond to pegylated interferon therapy currently being managed?

KM For the most part, these patients are being managed just by following them, as there are no other approved treatment options for children with HCV infection. If patients are eligible (depending upon the unique criteria of each trial), they may be enrolled into clinical trials with direct-acting antiviral agents. Clinical trial investigators are generally open to taking referrals of patients from other centers who would like to participate, as long as the participants are able to comply with the requirements of the trial.

G&H According to the data released to date from these clinical trials, how effective do direct-acting antiviral agents appear to be in HCV-infected children?

KM Thus far, data published on 12 weeks of sofosbuvir and ledipasvir (Harvoni, Gilead) in HCV genotype 1 subjects ages 12 to 17 years demonstrate a sustained virologic response of 98% at 12 weeks; 2 of 100 subjects were lost to follow-up and were counted as nonresponders. At 4 weeks, prior to the 2 subjects being lost to follow-up, sustained virologic response was 100%. Treatment of younger age groups with HCV genotype 1 is currently underway using this treatment regimen.

In addition, in HCV genotype 2 (12 weeks) and 3 (24 weeks) subjects ages 12 to 17 years, treatment with sofosbuvir (Sovaldi, Gilead) and ribavirin led to sustained virologic response of 100% at 4 weeks. Sustained virologic response was also 100% at 12 weeks for HCV genotype 2 subjects, but it was 97% for HCV genotype 3 subjects (1 of 37 subjects was lost to follow-up).

G&H Have there been any adverse events or safety concerns in these pediatric clinical trials thus far?

KM There have not been any serious adverse events to date. Adverse events occurring in 10% or more of treated teen subjects have included abdominal pain, headache, nausea, vomiting, diarrhea, fatigue, cough, and oropharyngeal pain.

When conducting clinical trials in children, there are almost always some safety data already known from adult trials with the given medications. In general, children tolerate medications better than, or at least similarly to, adults. Despite these reassurances, it is important to remember that the metabolism of children may be different from that of adults, and drug effects may be further influenced by weight, area of distribution, or surface area differences. Thus, pharmacokinetics and pharmacodynamics in different age groups are important to study with new medications, and doses for children should be determined physiologically and not simply based on what they were for adults.

G&H Is a pediatric indication expected soon for these agents?

KM Yes. For example, Gilead has already submitted an application to the US Food and Drug Administration for approval of sofosbuvir and ledipasvir for the treatment of HCV infection in children ages 12 to 17 years.

G&H How is quality of life affected in children with HCV infection?

KM Quality of life is an important issue in these patients. We know that HCV infection in adults is associated with decrements in quality of life, cognitive performance (especially attention and higher executive functioning), and psychological functioning (such as anxiety and depression). There have been several studies looking at similar indicators in children. A study of 19 children infected with HCV found that there was a decrease in global health and parental emotion in comparison to healthy, noninfected children. In addition, the infected children reported reduced physical functioning, although they did not complain of any specific symptoms, and parents were concerned about the future health of their children.

A larger study, conducted by Rodrigue and colleagues, used a number of psychological inventory tools in 114 HCV-infected children (mean age of 10 years) and compared the results to those of a normative pediatric population, as well as a population of children with other chronic conditions, specifically children with attention deficit hyperactivity disorder (ADHD) and children with chronic liver disease who were undergoing evaluation for liver transplantation. The researchers found that the children with HCV did not have global impairment in quality of life or cognitive, behavioral, or emotional functioning. Similarly, symptoms of stress, depression, and anxiety were not pervasive in children and adolescents with HCV infection, unlike in adults. However, approximately 20% of HCV-infected children had executive function impairments, which exhibited in their ability to plan, organize, and inhibit their own behaviors. In addition, children with HCV infection had worse cognitive functioning than the normal comparative group, although not as bad as children with ADHD. Another noteworthy finding is that the primary caregivers did not experience any decrements in quality of life generally; however, HCV-infected mothers had compromised quality of life compared to noninfected caregivers. This is important to point out because 60% of infected children contract HCV from their infected mother. All caregivers of HCV-infected children reported higher stress and concern over their child's health, believing that it would deteriorate, and reported that HCV infection had a negative impact on the overall functioning of the family.

G&H Are there any restrictions or precautions that are recommended for HCV-infected children?

KM All children infected with HCV should be vaccinated for hepatitis A virus as well as hepatitis B virus, which are vaccines universally recommended for children anyway. Additionally, HCV-infected children should not share with others anything that is likely to transmit blood, such as toothbrushes or razors, which is a good recommendation for all people.

G&H Do you anticipate that most medical insurance companies will pay for treatment with the direct-acting antiviral medications for children infected with HCV?

KM The financial impact of HCV infection in a person's lifetime vs the cost of treatment is very important. Right now, insurance companies are commonly not approving HCV medications without evidence of advanced fibrosis and/or an extenuating circumstance. Because of these limitations, most children with HCV infection do not qualify, and even patients over the age of 18 years, in whom the direct-acting antiviral medications are currently approved, are being denied. Doctors and families do not want to wait for treatment until the liver is fibrotic. Thus, it is important to understand the impact and cost of living with the infection, dealing with disease progression and the possibility of developing advanced liver disease vs treating children when they are young, before the negative impacts of HCV infection develop.

G&H What are the next steps in research in terms of the management of HCV-infected children?

KM Most active ongoing research involves examining the efficacy and tolerability of the new HCV drugs in the pediatric population. It is important that this research continue so that these drugs can become available and ultimately approved for children as appropriate. Another important area of research involves better understanding of the immunologic response in viral hepatitis as well as further understanding of the mechanisms that lead to viral clearance vs chronic infection.

Dr Murray receives research funding from Gilead and owns Merck stock.

Suggested Reading

Balistreri WF, Murray KF, Rosenthal P, et al. The safety and effectiveness of ledipasvir-sofosbuvir in adolescents 12 to 17 years old with hepatitis C virus genotype 1 infection [published online December 20, 2016]. *Hepatology*. doi:10.1002/hep.28995.

Jonas MM, Balistreri W, Gonzalez-Peralta RP, et al. Pegylated interferon for chronic hepatitis C in children affects growth and body composition: results from the pediatric study of hepatitis C (PEDS-C) trial. *Hepatology*. 2012;56(2):523-531.

Jonas MM, Schwarz KB, Gonzalez-Peralta R, et al. Long-term growth outcomes in children treated for chronic hepatitis C. *J Pediatr*. 2014;165(6):1252-1254.

Rodrigue JR, Balistreri W, Haber B, et al. Peginterferon with or without ribavirin has minimal effect on quality of life, behavioral/emotional, and cognitive outcomes in children. *Hepatology*. 2011;53(5):1468-1475.

Schwarz KB, Molleston JP, Jonas MM, et al. Durability of response in children treated with pegylated interferon alfa 2a ± ribavirin for chronic hepatitis C. *J Pediatr Gastroenterol Nutr*. 2016;62(1):93-96.