Chapter 6.1. Pediatric Chronic Hepatitis B and C: 30 Years of ESPGHAN Clinical Research and Recommendations

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ABSTRACT

The expression of hepatitis B and C virus infections in children differs from that in adults and requires specific paediatric expertise. The European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) has been a pioneer in this field, having stressed the need for straightforward recommendations since the mid-1980s. Following much observation, surveillance, and research, a panel of ESPGHAN experts was able to develop such recommendations on hepatitis B infection in children in 2009, which was then followed in June 2013 by proper guidelines. In the field of Chronic Hepatitis C, in 2011 ESPGHAN experts published also the Guidance for Clinical Trials for Children and Adolescents, and approved in 2012 the NASPGHAN guidelines for treatment. The ESPGHAN Society is to be commended for its pioneering work in furthering our understanding of chronic hepatitis B and C disease presentations in infants, children, and adolescents.

Key Words: Chronic Hepatitis B, Chronic Hepatitis C, children, recommendations

(*JPGN* 2018;66: S119–S121)

HEPATITIS B

Epidemiology and Natural History

Hepatitis B virus (HBV)–related chronic hepatitis (CHB), defined as positive HBsAg for ≥6 months, is typically asymptomatic in childhood. Nevertheless, 25% of all HBV chronic carriers worldwide exhibit a life-long risk of developing hepatocellular carcinoma (HCC), with an incidence of cirrhosis of 2% to 3% per year (1). HBV is transmitted through exposure to infectious blood, semen, vaginal secretions, and saliva (2). The infection prevalence has been declining worldwide since 1991, when the World Health Organization (WHO) called for all countries to incorporate HBV vaccinations in national immunization programs (3,4). Additionally, strict blood-donor and pregnant women screenings have been instrumental in decreasing the prevalence. Ten HBV genotypes (A–J) have been reported, with genotype A predominant in Europe, while genotypes B, C, D, and F are more common in high/intermediate HBV prevalence countries (5–7). In Western countries the vertical transmission is prevalent (8). Vertical-infected infants become immunotolerant to the virus and develop a lasting asymptomatic infection, characterized by high viral replication yet no liver injury. Nevertheless, these infants exhibit a 90% risk of developing CHB, and 25% will die from chronic liver disease during adulthood.

Treatment

Since the mid-1980s, the ESPGHAN society has been pushing for straightforward recommendations to clarify who needs to be treated and when to start the treatment. Management proposals were published by an expert group in 2009 (9), with proper guidelines published in 2013 by a panel of ESPGHAN experts (10) who developed a treatment algorithm to assist practitioners in their decision-making process. Antiviral treatment should be considered for children with high ALT levels for at least 6 months, an indirect marker of ongoing liver injury, in order to avoid treating patients undergoing spontaneous HBeAg seronconversion. Since the upper limit of normal (ULN) for ALT in children has not been established, ESPGHAN guidelines recommend those patients to be considered for antivirals if ALT levels exceed 1.5 times the laboratory ULN. In the presence of high ALT levels, the assessment of serum HBV DNA is required, with high HBV DNA values warranting antivirals, whereas low levels require further investigations to exclude other causes for liver injury. Other factors must be considered prior to initiating therapy: liver histology, family HCC history, coexisting liver diseases, and prior treatments (10). Antivirals are indicated in children undergoing liver transplantation, while prophylactic administration is recommended for HBsAg-positive patients due to receive immunosuppressive or cytotoxic therapy (11,12). The Food and Drug Administration (FDA) has approved 6 medications for treating CHB in children: interferon-alfa (IFNα) and pegylated interferon-alfa (PEG-IFNα), lamivudine, adefovir, entecavir, and tenofovir, with all these drugs tested in children in multicenter ESPGHAN-NASPGHAN (North American Society for Pediatric Gastroenterology, Hepatology and Nutrition) trials.

IFNα, the first drug approved for CHB in children, is associated with a virological response (VR: undetectable HBV DNA and HBeAg clearance) in 26% of IFNα-treated children after 24 weeks versus 11% of untreated controls (12). This response rate increases to 35% when only patients with elevated ALT levels are considered. HBsAg clearance is noted in 10% of treated children versus 1.2% of controls. Response probability is shown to be associated with low baseline HBV DNA, younger age (<5 years old), and female gender (13). In early years, IFNα was presumed to accelerate HBeAg seroconversion, and it was confirmed by 3 studies, though with similar long-term HBeAg clearance rates between treated and untreated patients (14–16). Despite having no long-term consequences, IFNα therapy is shown to cause transient impairment of growth. Today IFNα administration is recommended in HBeAg-positive children aged ≥2 years, with abnormal ALT and low-intermediate HBV DNA levels. Several

Received January 28, 2018; accepted January 29, 2018.

DOI: 10.1097/MPG.0000000000001916

trials were implemented by ESPGHAN–NASPGHAN members in order to assess nucleotide/nucleoside analogues in CHB children with multiple European and US centres involved. Lamivudine was the first nucleoside analogue to be FDA-approved for CHB treatment in children aged ≥3 years. VR is achieved in 23% of patients, in 34% if considering patients with elevated ALT levels (17,18). Lamivudine's essential limitation is the risk of developing lamivudine-resistant mutations in the tyrosine-methionine-aspartate-aspartate (YMDD) viral locus. Combination of lamivudine and IFNα in immunotolerant patients is shown to achieve 17% rate of complete viral control (HbsAg loss) (19). Adefovir dipivoxil, a purine analogue, was FDA-approved in 2010 for treating CHB children aged ≥12 years. VR is achieved in 23% of patients aged 12 to 17 years. Compared to lamividune, adefovir offers a major advantage of proving effective against all hepatitis B viruses, including lamivudine-resistant strains, and in the long run adefovir resistance rates are lower (20). Moreover, adefovir appears to be effective in HBeAg-negative hepatitis. Entecavir, a carbocyclic analogue of 2′-deoxyguanosine, is active on both lamivudine-resistant and adefovir-resistant strains. It is approved by FDA for children ≥2 years old, and it is effective in inhibiting viral replication, but only patients with HBeAg seroconversion are likely able to discontinue treatment without relapse, thus this may require several years of treatment. VR is reported in 24% of patients after 48 weeks (21), significantly associated with lower DNA (<8 log10), transaminase levels >2 × ULN, and genotype A/C. Based on these data, ESPGHAN now recommends to carefully select candidates eligible for treatment. Tenofovir, a nucleotide analogue similar in structure to adefovir but less nephrotoxic, is among the first-line treatments for adult CHB, along with PegIFN and entecavir. Like entecavir, tenofovir has proven to be effective against lamivudine-resistant mutations. Tenofovir was investigated in children aged 12 to 18 years old, with 89% of them achieving VR. However, after 72 weeks of therapy, HBeAg-Ab seroconversion rate was not higher in the treated patients as compared to placebo (22). Telbivudine, a L-nucleoside analogue, was approved by FDA in 2006 for children ≥16 years. In comparison with adefovir and entecavir, resistance rates for telbivudine have proved to be higher, increasing with the duration of treatment.

New antiviral approaches that target various steps and components of the HBV lifecycle are being investigated, with the hope of a complete viral eradication. These approaches include HBV entry inhibitors, such as Myrcludex B, a lipo-myristolated peptide mimicking the pre-S1 domain that competes with HBV particles to bind to the sodium taurocholate co-transporting polypeptide (NTCP). Studies on the drug's safety carried out on healthy adults showed modest and transient elevations of amylase and lipase, without clinical relevance in a low percentage of patients (18). Studies on paediatric population could be crucial on eradicating HBV infection in children.

HEPATITIS C

Epidemiology and Natural History

With the availability of HCV treatments in the early 1990s, the incidence rate of HCV infection has significantly decreased in the last 2 decades, nevertheless the number of deaths per year due to HCV liver disease (cirrhosis, hepatocellular carcinoma and liver failure) is constantly increasing. Eleven million of infected people are younger than 15 years of age, of whom 5 million are viremic. Up to now, 7 genotypes (1–7) have been reported, with genotype 1 the most prevalent worldwide (46.2%, 83.4 million), counting for the majority of HCV infections in developed countries. After the universal screening of blood products, vertical transmission is the most common route of acquiring HCV in infants and children in developed countries, while in developing countries contamination through transfusion or health care procedures is still common. The prevalence of HCV infection in children in developed countries ranges between 0.1% and 0.4%, while it is lower in high-income countries (0.05%–0.36%) (23–25). The rate of perinatal transmission from an infected mother to her child ranges from 2% to 5%. Among vertically infected children, HCV infection is shown to chronicize in 80% (26–27). Children with HCV infection differ from adults in several ways including modes of transmission, rates of clearance, progression of fibrosis, and the duration of potential chronic infection when acquired at birth. Infected children are usually asymptomatic, with a low risk of progression of the disease, but almost 5% of them develop significant liver disease in childhood.

The incubation period for HCV infection can range from 2 weeks to 6 months. More than three-quarters of HCV-infected children and adolescents are asymptomatic, with normal or only mildly increased serum ALT levels. Nonspecific signs and symptoms (hepatomegaly, hyperpyrexia, lethargy, anorexia, nausea, vomiting, abdominal colic, deep-coloured urine, light-coloured faeces, arthralgia, and yellowish discoloration of skin and sclera) can occur in approximately 15% of paediatric population.

Treatment

In 2012 ESPGHAN/NASPGHAN guidelines on ''Diagnosis and Management of Hepatitis C Infection in Infants, Children, and Adolescents'' suggested to start treating children with hepatitis C who demonstrate persistently elevated serum aminotransferases or those with progressive disease (ie, fibrosis on liver histology). Peg-IFN and ribavirin were approved by the FDA (2008) and the EMA (2009) for children aged more than 3 years. The rate of SVR is lower in case of genotype 1, the most prevalent HCV genotype globally, which 48 weeks-treatment results in a sustained virologic response (SVR) in <50% of children (28). In the case of genotype 4 SVR rate is achieved in 40% to 69% of children after 48 weeks of therapy (29). ESPGHAN/NASPGHAN guidelines recommend treatment of patients with genotype 1 and 4 for 48 weeks, patients with genotype 2 and 3 for 24 weeks. However, this regimen is burdened with consistent adverse effects: pyrexia, headache, gastrointestinal symptoms, depression, neutropenia and haemolytic anaemia, including deleterious effects on growth (30–33). Furthermore, the use of IFN for the treatment of HCV has been traditionally contraindicated in decompensated cirrhosis, leaving these patients at even greater risk for the development of end-stage liver disease. Given these assumptions, additional treatment options are still needed to eradicate the infection, with better SVR, especially for genotype 1, and less adverse effects. For this purpose, in 2011 an ESPGHAN committee published the ''Guidance for Clinical Trials for Children and Adolescents with Chronic Hepatitis C'' (28).

Modern direct antiviral agents (DAA) have revolutionized therapy of HCV infection and are now preferred for treatment in adults. The combination multiple classes of HCV antivirals is shown to reduce the development of viral resistance and improves SVR rates. The fixed dose once-daily-single-tablet- regimen of sofosbuvir (an inhibitor of the NS5B RNA-dependent RNA polymerase) and ledipasvir (an inhibitor of the NS5A protein) has been approved for the treatment of chronic HCV genotype 1 in patients aged >18 years in December 2013. This combination is shown to lead to SVR rates of >95% in HCV-genotype 1–infected patients, not only treatment naive but also with prior treatment experience. Phase II and III trials of combination DAAs, including the fixed-dose combination sofosbuvir and ledipasvir, for children aged 3 to 17 years with chronic HCV is currently ongoing (34). Safety results have shown comparable pharmacokinetics parameters and safety profiles between adult and adolescent populations with HCV

infection, and first patients treated confirm similar pharmacokinetics and efficacy before and after paediatric liver transplantation (35). Mild and inconstant adverse effects are reported in adults, not affecting the final outcome (36).

CONCLUSIONS

HBV and HCV infections are still a major issue worldwide. Current treatments available for paediatric population are partially efficient in curing the diseases and burdened with several adverse effects. New treatment options, such as new drugs blocking viral entry via the NTCP receptor and modern DAA need to be designed for HBV for HCV-infected children respectively. Long-term studies remain a must to better apprehend the natural history of these infections, along with the treatments' impact.

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