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DAA therapy for HCV-infected children

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Q. What is the burden of early life infection with HCV?

In 2014 it was thought that over 11 million children <15 years of age in the world have been infected with HCV and at least 6 million of these were viremic and in need of treatment[1]. However, most recent estimates have reported a decrease in the amount of infections globally to about 3.5 million children 1-15 years of age[2, 3]. The prevalence of HCV is particularly high in Central and East Asia, Northern Africa, and the Middle East. Children who are refugees from these areas are likely to have a higher rate of infection compared with those from other regions of the world[4]. The prevalence of HCV in children in low-income countries is about 0.6% whereas in contrast, the figure is 0.3% in high income countries[4]. The prevalence of HCV infection in children is higher in high-risk children such as the homeless and those who inject drugs, the opioid epidemic has brought with it an increased number of young adults infected with HCV. This epidemic has resulted in a 3.8-fold increase in HCV-infections in young adults 20 – 39 years of age[5], females in this demographic are at risk for giving birth to HCV-infected newborns.

Q. Why is treatment of HCV deemed necessary and what is the current standard of care?

Treatment of HCV in children is necessary for multiple reasons: to decrease the lifetime risk of chronic liver disease, cirrhosis, need for liver transplantation and/or hepatocellular carcinoma, to decrease child and family anxiety and stigma, to decrease the small but real risk of horizontal transmission and the real risk that the untreated female child will become an infected adult of child-bearing age who, when pregnant, carries the risk of maternal-infant transmission of about 5%.[1]

The Hepatitis Expert Team of the Federation of International Societies of Pediatric Gastroenterology, Hepatology and Nutrition (FISPGHAN) has recently reviewed recommendations for the treatment of HCV infected children published by various medical societies[6]. All agreed with implementing DAA therapy for adolescents 12-17 years of age and deferring treatment for children 3-11 years of age. However, since acceptance of that article for publication, DAA therapy for children 3-11 years of age has been approved. There are no recommendations for treatment of children <3 years of age, in part because there is a reasonably high spontaneous viral clearance before age 3 years with a lower chance of that happening after age 3 years.

In 2017 the first DAA regimes for children 12-17 years of age were approved: sofosbuvir/ledipasvir for genotypes 1, 4, 5 and 6 and sofosbuvir/ribavirin for genotypes 2 and 3. In 2019 approval for these drugs was extended to children 3-11 years of age. Two DAA regimes with pangenotypic efficacy have been approved for children: glecaprevir/pibrentasvir; and sofosbuvir/velpatasvir. All of these regimes have very high safety and efficacy (>90-95% sustained viral response) and are much better tolerated than pegylated interferon/ribavirin which was approved for use in children from the US Food and Drug Administration several years earlier. Therefore, international organizations such as the World Health Organization and the American Association for the Study of Liver Diseases have recommended against the use of interferon-based regimes for children <12 years of age[6].

The FISPGHAN paper reviewed differences in societal recommendations for the treatment of children with compensated cirrhosis and genotype 1 (12 vs 24 weeks treatment). Another difference is that some organizations recommend sofosbuvir/ribavirin for genotypes 2 and 3 and others recommend the pangenotypic sofosbuvir/velpatasvir[6]. Finally, there are organizational differences in recommendations for adolescents: for those 12-17 years of age and >35 kg, ledipasvir/sofosbuvir and sofosbuvir/ribavirin are recommended by the WHO and ESPGHAN whereas AASLD recommends for adolescents 12-17 years of age and >45 kg, ledipasvir/sofosbuvir, sofosbuvir/ribavirin or glecaprevir/pibrentasvir[6].

Q. To what extent has DAA therapy for infected children supported the campaign for viral hepatitis elimination?

The World Health Organisation (WHO) recently set the goal to decrease, by 2030, chronic hepatitis virus infections drastically to 0.9 million and to reduce the annual deaths from chronic hepatitis to less than 0.5 million[7]. Elimination of viral hepatitis as a major public health threat is the major objective. It is currently estimated that 184 million persons in the world are infected with HCV; thus reducing this number to less than 0.9 million is an enormous challenge. It is important to know that unlike the case with hepatitis B, there is no way at present to interrupt the transmission of HCV from mother to infant; also as mentioned above, the spontaneous viral clearance of HCV in the young is low, about 20-30% at best, and usually does not occur after 3 years of age.[4] Therefore for all practical purposes if we are to achieve the goal of elimination of viral hepatitis, we need to treat all HCV-infected children who are eligible for treatment. There are several advantages of treating young subjects; they generally live in a controlled environment in which treatment can be administered under the supervision of parents or caregivers, they have less advanced liver disease, and since the drugs are dosed according to body weight, smaller children need smaller amounts of drug.

Q. Is any antiviral treatment available to prevent mother to child transmission at birth?

There are no published clinical trials of antiviral treatment during pregnancy for this purpose. Cervino and Hynicka[8] have suggested that given the absence of data in this setting as well as the availability of safe effective antiviral agents for young children, that antiviral treatment during pregnancy should not be undertaken and that treatment should be deferred until the child reaches the age when approved treatments are available. Pfeiffer et al.[9] have examined placental drug transporters in 4 HCV-infected women and observed increased expression of P-gp and BCRP. The authors hypothesized that this increased expression would limit the maternal-fetal transport of antiviral drug substrates across the placental barrier but they acknowledged much more data in larger numbers of HCV-infected women and a larger variety of drug transporters was sorely needed before firm conclusions could be reached. Mandmika et al.[10] did use sofosbuvir monotherapy to treat an HIV-HCV infected woman during the second trimester of pregnancy with resultant clearance of HCV in the woman and birth of an infant who was HCV negative at birth and remained so at two years of age. As yet there are little data regarding the efficacy of DAA's in the third trimester to prevent maternal fetal transmission. Clearly much more data are needed on both placental drug transporters as well as carefully constructed pilot trials of DAA's in the third trimester in which the risk of teratogenicity would be minimal.

However if the goal of global eradication of HCV is to be reached it would be important to embark on aggressive attempts to focus on elimination of HCV infection in children, by screening and treating high-risk children and adolescents as well as continuing the important studies of how best to target inhibition of maternal-infant transmission which remains the major source of HCV infections in the pediatric age group.

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