

## Sofosbuvir in Paediatric Population - A Clinical Update

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Dear Madam,

With the development of a new regimen for treatment of hepatitis C viral infection, the idea of eradication of the fatal virus seems not too far-fetched. The availability of oral hepatitis C virus direct-acting antivirals ensure safe and effective treatment for adults with hepatitis C infection. However, treatment with these drugs has not yet been approved for children under the age of 12 with chronic hepatitis C. Pegylated interferon and ribavirin remain the only choice of drugs to treat paediatric population. Trials assessing the safety and efficacy of direct-acting antivirals in paediatric age group are currently in progress. Thus, I am writing to your revered journal to update the readers on the progress made towards the treatment of hepatitis C in children in terms of available regimen and the new drugs under trial.

With a burden of approximately 71 million people, hepatitis C is a serious global issue. The fatal liver disease which can progress to liver cirrhosis and liver cancer claims approximately 39,900 lives each year<sup>1</sup>. When the treatment of choice is concerned, the preferred regimen for chronic hepatitis C has rapidly changed. For a long time, the standard treatment included pegylated interferon alpha-2a (PEG-IFN- $\alpha$ ) and ribavirin for up to 48 weeks for genotype 1 and PEG-IFN- $\alpha$  and ribavirin for 24 weeks for genotypes 2 and 3<sup>2</sup>. The success

of drug therapy depends upon the genotype as well as the number of patient who go untreated either due to contraindications (advanced hepatic disease, autoimmune disease and psychiatric illness) or due to poor compliance, owing to a long duration of treatment, their need to be injected and adverse effects (fatigue, fever, headache, cytopenia, autoimmune disorders, insomnia and depression). Protease inhibitors included in the therapy, while decreasing the duration of treatment, limit the efficacy because of low genetic barrier to resistance, more side effects and complex regimen<sup>3</sup>.

Direct-acting antiviral (DAA) are the class of drugs that target specific non-structural proteins of virus which results in disruption of viral replication and infection. With the advent of DAA the treatment of hepatitis C has transformed greatly. World Health Organization (WHO) includes DAA in its preferred regimen with a cure rate achievable to up to 90%<sup>1</sup>. Sofosbuvir, due to its low side effects, oral administration, high potency, shorter duration of treatment and high barrier to resistance has gained particular interest among DAAs. The United States Food and Drug Administration (FDA) approved sofosbuvir in 2013 for treatment of chronic hepatitis C (CHC), in combination with ribavirin, or in combination with PEG-IFN- $\alpha$  and ribavirin. The efficacy of sofosbuvir has been established in subjects with hepatitis C virus (HCV) genotype 1, 2, 3 and 4. However, FDA has not approved sofosbuvir for treatment of CHC in children as its efficacy and safety has not yet been determined.

When children are considered, HCV manifests itself differently than how it does in adults. Children may often remain asymptomatic, may clear virus spontaneously and maintain normal levels of alanine

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aminotransferase (ALT)<sup>5</sup>. Hepatitis C in childhood can lead to cirrhosis and liver failure in adulthood necessitating an early intervention<sup>6</sup>. FDA has approved Sovaldi (sofosbuvir) and Harvoni (ledipasvir and sofosbuvir) to treat HCV in children ages 12 to 17. Harvoni is indicated for paediatric patients from 12 years of age and older or weighing at least 77 pounds with genotype 1, 4, 5 or 6 infection, without cirrhosis or with mild cirrhosis, while Sovaldi is indicated in combination with ribavirin for treatment of paediatric patients from 12 years of age and older or weighing at least 77 pounds with genotype 2 and 3 infection without cirrhosis or with mild cirrhosis<sup>7</sup>.

Furthermore, for children less than 12 years of age, trials are under progress. An open label study is recruiting participants. The purpose of this study is to evaluate the pharmacokinetics and age-appropriate dose responses of sofosbuvir for paediatric patients in combination with ribavirin as well as evaluating the safety, efficacy and tolerability of sofosbuvir plus ribavirin for 12 weeks in children with HCV genotype 2, or 24 weeks for those with genotype 3<sup>8</sup>. Another such study evaluating a fixed dose co-formulation of sofosbuvir/ledipasvir without ribavirin in children and adolescents with CHC is also recruiting participants<sup>9</sup>. The Health-Related Quality of Life in Adolescent Patients with Hepatitis C Genotype 1 treated with Sofosbuvir and Ledipasvir has recently been published<sup>10</sup> and this may indicate optimism in treating children with confidence of the mentioned medications with less side effects compared to the routine PEG-IFN- $\alpha$  and ribavirin.

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