Chronic Hepatitis C: Do Generics Work as Well as Branded Drugs?

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India has a large share of the hepatitis C virus (HCV) burden of the world. Unsafe medical practices and blood transfusions are the leading modes of transmission of HCV in India. The commonest HCV genotype in India is genotype 3 followed by genotype 1. While directly acting antivirals (DAAs) agents have become available at reasonable rates in India, cost of therapy remains a major barrier for control of HCV in India. Generic DAAs have been proven to be cost-saving in prior studies. We examined data from various studies in India and elsewhere using generic DAAs, and evaluated whether they are equally efficacious as the branded drugs. Since the availability of generic DAAs in the Indian market, there is a lot of real life data as well as prospective studies in special patient populations such as hematological disorders (thalassemia and hemophilia), chronic kidney disease, hemodialysis patients, post liver and renal transplant patients on immunosuppression, intravenous drug users, confections and other high risk groups. Control of HCV infection in India requires multi pronged approach. There is a need to formulate a health educational curriculum targeting not only the high-risk population but also the general population regarding the transmission of HCV. Adopting the dual approach of treating the old cases (decreasing the reservoir pool of HCV) and decreasing the incidence of new ones would help curtail the disease and decrease liver related mortality. In this scenario, the role of efficacious low cost generic medications is essential. (J Clin Exp Hepatol 2017;7:253–261)

The prevalence of hepatitis C virus (HCV) infection is estimated to be more than 70 million people worldwide and between 6 and11 million in India.[1] Chronic HCV infection is one of the prevalent causes of the disease burden of cirrhosis, hepatocellular carcinoma (HCC) and liver-related deaths in India. Untreated HCV infection also leads to substantial economic burden and a hidden social cost.[2] Despite a low to moderate (1–1.5%) prevalence of HCV, India accounts for a significant share of global HCV infections due to the large population; approximately 12–18 million population is infected with HCV. In 2015, about 60,000 deaths were reported to be related to HCV alone in India.[3]

New directly acting antivirals (DAAs) for HCV treatment are efficacious, providing rates of sustained virological response (SVR) exceeding 95%.[4] However the patented drugs are expensive limiting treatment to those with advanced disease. Thus, these drugs offer a hope of reducing the burden of HCV, reducing disease transmission and complications of liver disease. Hence, in India a dual approach reducing incidence and increasing treatment is appropriate in showing short-term improvements in advanced stage outcomes with reductions in prevalence.[1] However, these drugs are very costly in several countries.[5] In India, the three DAAs [sofosbuvir (SOF), ledipasvir (LDV) and daclatasvir (DCV)] are available from several generic manufacturers at a price as low as $110 for 12 weeks therapy.[6] This is in stark contrast to the cost of 12-week sofosbuvir therapy being approximately US $42,017, ranging from US $37,729 in Japan to US $64,680 in the United States.[5] In a recent report, the use of generic DAAs in Indian hepatitis C patients was reported to increase the life expectancy by 8.02 years, increase quality-adjusted life years (QALYs) by 3.89, avert 19.07 disability-adjusted life years (DALYs), and reduce the lifetime healthcare costs by $1309 per-person treated, when compared with untreated HCV infected patients.[7] Treatment became cost-effective within 2 years, and cost-saving within 10 years of its initiation in all subjects and within 5 years in patients with cirrhosis.[7] Almost all published cost and efficacy analyses have been conducted in developed nations under patent rules where DAAs have a prohibitive cost limiting widespread use.[9–11] The efficacy of generic DAA is under scrutiny, and in this study we report the pooled data from different trials in India and

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Abbreviations: ALT: alanine aminotransferase; CHC: chronic hepatitis C; CI: confidence interval; DAAs: direct-acting antiviral agents; DCV: daclatasvir; EASL: The European Association for the Study of the Liver; GT: Genotype; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; IL: interleukin; INASL: Indian National Association for study of the Liver; LDV: ledipasvir; Peg-IFN: pegylated interferon; RBV: ribavirin; SOF: sofosbuvir; SVR: sustained virologic response; VEL: velpatasvir

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elsewhere using sourced generic DAA therapy. We found generic DAA to be cost-effective in view of low treatment prices and also be cost-saving in terms of improvement of both public health burden and economic cost perspective. The Mukh Mantri Punjab Hepatitis C Relief Fund (MMPHCRF) is a public health initiative by the government of Punjab to tackle the HCV burden in the state (http://pbhealth.gov.in/SOPs%20for%20MMPHCRF.pdf).[12] The results from this treatment program will drive physicians and public health professionals toward central funding of HCV treatment, and may make it easier for health administrators and political leaders take an informed decision. We therefore estimated the efficacy of treatment of HCV-infected persons in India and else where using low-priced DAAs, and evaluated the results from various published and unpublished clinical data from different centers across the country. This question is also of interest for other countries where it may be possible to obtain DAAs at low prices.

MANAGEMENT OF HCV IN INDIA

In India, pegylated interferon alfa (Peg-IFNα) plus ribavirin (RBV) combination therapy has been replaced by DAAs. These drugs have lower side effects, better tolerability, and are simpler to administer. In view of their potential efficacy and safety (SVR > 90% in most studies), DAAs have the potential to eliminate one of the most common causes of liver related morbidity and mortality.[12] The nucleoside non-structural protein non-structural (NS) 5B inhibitor SOF became available in India in March 2015, which was followed in 2016 by the NS5A replication complex inhibitors, LDV and DCV. Velpatasvir (VEL), a pangenotypic DAA, is now available in India and the Indian National Association for Study of the Liver (INASL) guidelines are accordingly going to be updated. The INASL guidelines are based on considerations for the treatment of HCV in India including the cost of therapy, the poorer response of the predominant genotype (GT 3) and the non-availability of many of the DAA recommended by other guidelines.[4,5] The widespread uptake of DAA in India is possible, as these have so far been marketed at a fraction of the cost in the west.

COST EVALUATION OF DAAS

Aggarwal et al.[7] have presented a model for healthcare payer's perspective. For effectiveness outcomes, they used QALYs, a commonly used metric in cost-effectiveness analysis, and DALYs, as recommended by the WHO. The cost of SOF/LDV (with or without RBV), or SOF/DCV combination treatment was taken as Indian Rupees (INR)approximately 6711 (USD 100) for every 28 days' supply. The costs of pre-treatment testing (for disease staging and HCV genotyping) were taken as INR 8000 (approximately USD 119), and those for tests while on and after treatment were taken as INR 6000 (approximately USD 89). The authors presented a minimalistic cost model representing a conservative scenario by underestimating the savings resulting from DAA use; however, this was supplemented by sensitivity analyses using a wide range of costs.[7] A recent pharmacoeconomic study established that the use of generic DAAs in Indian HCV patients would increase the life expectancy by 8.02 years, increase QALYs by 3.89, avert 19.07 DALYs, and reduce the lifetime healthcare costs. Treatment became cost-effective within 2 years, and cost-saving within 10 years of its initiation overall and within 5 years in persons with cirrhosis.[8,9]

The high cost of patented DAA drugs needs to be reevaluated in the setting of cheaper and efficacious generic alternatives. The business model relies on using patent protection laws against free market competition with little revenue being directed at new drug research, with more stress on drug marketing (25% of revenues) rather than new drug discovery (1.3% of revenues).[10] Generic versions of DAAs are manufactured in India under voluntary license from Gilead Sciences, and by other Indian companies who are not licensees, and in other countries which are not bound by patent law. In many countries it is legal to import drugs for personal use by ordering them online. In other countries imports of generic drugs are restricted to those carried through customs by individuals in quantities sufficient for personal use. Hence over the last two years a large pool of data has emerged from India, the Middle Eastern countries and also 'buyers' clubs' in the west using imported generic medicines.[13] Bioequivalence studies also establish efficacy of generic medications. A test group of 25–50 subjects takes a single dose of originator medication, and the blood levels of the drug(s) are measured at various time points over the next 24 h. After a washout period, the same group then takes the generic version and once again the blood levels of the drug(s) are measured. A drug is deemed bioequivalent when the blood levels at all time points are a statistically near identical match. Bioequivalence proves, not only do the tablets contain the active ingredient(s) in the correct quantity, but more importantly that they deliver these into the patient's system in a similar fashion to the originator version.[14] Preliminary reports of the generic DAA have shown reasonable results (Table 1).

Hill et al reported people who purchased the drugs were cured of hepatitis C at a cost of around $700–$900 in South-East Asia and Eastern Europe. The price of treatment remains a major barrier to curing hepatitis C for millions of people, and where rationing of treatment, lack of health insurance or lack of a national treatment program deny access to these drugs, people are turning to internet-based community portals or 'buyer's clubs' to obtain generic versions of direct-acting antivirals.[20–23] Freeman et al.[23] showed very high cure rates when using

