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Retrospective Study

Generic *vs* brand forms of direct acting antivirals for hepatitis C virus treatment in Egyptian children

Mogahed E *et al*. Generic *vs* brand forms of DAAs for HCV treatment

Abstract

BACKGROUND

Direct acting antivirals have revolutionized hepatitis C virus (HCV) treatment. However, the high price of the brand forms is a barrier for their use in resource limited countries as Egypt.

AIM

To assess the safety and efficacy of the generic sofosbuvir (SOF)/ledipasvir (LED) in Egyptian HCV-infected children and to compare the results with the brand form.

METHODS

This analytical retrospective study included HCV infected children and adolescents aged 12-18 years or weighing > 35 kg. Collected data included: Age, sex, risk factors of HCV acquisition, comorbidities, liver functions, HCV viral load, degree of hepatic fibrosis, sustained virologic response (SVR) and frequency of treatment adverse effects. Patients who received the generic form of SOF/LED (Ledisbuvir) were compared to patients who received the brand form (Harvoni®) regarding SVR and frequency of adverse events.

RESULTS

The study included 43 patients who received Ledisbuvir and 73 who received Harvoni®. All patients achieved SVR. Treatment side effects were mild, transient and comparable in both groups.

CONCLUSION

The use of generic SOF/LED in HCV infected children is safe and effective. It is comparable to the brand form at a reduced price and represents an affordable and effective alternative.

Key Words: Children; Direct acting antivirals; Generic; Hepatitis C virus; Ledipasvir; Sofosbuvir

Mogahed E, Ghita H, Enayet A, Yasin N, El-Karaksy H. Generic vs brand forms of direct acting antivirals for hepatitis C virus treatment in Egyptian children. *World J Hepatol* 2025; In press

Core Tip: Direct acting antivirals have revolutionized hepatitis C virus (HCV) treatment. The high price of the brand forms is a barrier for their use in resource limited countries. The use of the generic forms of direct acting antivirals in adult treatment programs has increased treatment coverage and changed the disease burden. Scanty data are available for their use in children. Our findings support the use of the generic form of sofosbuvir/ledipasvir in HCV infected children. The comparable efficacy and safety outcomes to the branded Harvoni® regimen, coupled with the cost advantages of generics, reinforce their value in national HCV control strategies.

INTRODUCTION

Hepatitis C virus (HCV) infection represents a significant global health burden, with an estimated 58 million people chronically infected worldwide, including a substantial pediatric population. The advent of direct acting antivirals (DAAs) has revolutionized

the management of HCV, offering high cure rates, shorter treatment durations, and a favorable safety profile compared to the interferon-based regimens previously employed[1].

Among these DAAs, the fixed-dose combination of sofosbuvir (SOF) and ledipasvir (LED) has demonstrated excellent efficacy and tolerability in both adult and pediatric populations[2]. The brand formulation, marketed as Harvoni®, has achieved sustained virologic response (SVR) rates exceeding 95% in multiple clinical trials and real-world studies on HCV infected pediatric patients[2,3]. However, the high cost of the brand-name medication remains a major barrier, particularly in low- and middle-income countries like Egypt, where HCV prevalence tends to be higher[4].

To address these economic challenges and improve treatment accessibility, several generic versions of SOF/LED have been developed and approved in various regions. Clinical data from Egypt, China, India, and Argentina have shown SVR rates exceeding 90% with generic SOF-based regimens, alongside excellent tolerability profiles[5-11].

Egypt's national HCV elimination program now stands as the largest of its kind worldwide, successfully demonstrating that HCV can be efficiently cured through mass treatment initiatives. One of the keys to this success was the widespread availability of affordable generic medications, which enabled treatment scale-up[12].

While Egypt's adult population has benefited substantially from these advances, pediatric HCV management continues to lag. Limited published data exist regarding the comparative safety and efficacy of these generic formulations against the original brand in pediatric patients. The present study was designed to bridge this knowledge gap by providing real-world evidence on the safety and efficacy of a locally manufactured generic SOF/LED combination compared to the brand formulation in children and adolescents with chronic HCV infection.

MATERIALS AND METHODS

This single center retrospective analytical study included Egyptian HCV infected children and adolescents who received treatment with the generic or brand forms of

SOF/LED. The study was conducted at the Pediatric Hepatology Unit, Cairo University Pediatric Hospital, Cairo, Egypt. The study was conducted in accordance with Declaration of Helsinki and the study protocol was approved by Cairo University institutional review board and ethical committee, approval No. N-173-2024. The informed consent was waived because of the retrospective nature of the study.

The study included all children and adolescents with chronic HCV infection of both sexes, 12-18 years old or weighing > 35 kg (even if younger than 12 years) who presented to the Pediatric Hepatology Unit during the time period from 2017-2023. Patients with a history of hepatitis B virus infection, or patients with significant or unstable cardiac disease or uncontrolled cardiac arrhythmias were excluded from treatment.

The following data were collected from the patients' files: (1) Demographic data (age and sex); (2) Risk factors of HCV acquisition (*e.g.* maternal HCV, intrafamilial cases, blood product transfusion, hospitalization, operation, chemotherapy); (3) Comorbidities; (4) Medication history (including previous HCV treatment and current therapy for comorbidities); and (5) General, systemic and abdominal examination.

Results of baseline (pre-treatment) investigations recruited from patients' files included: Complete blood count, total and direct serum bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma glutamyl transpeptidase, serum albumin, international normalized ratio, serum creatinine, 12-lead electrocardiogram, echocardiography and Holter electrocardiogram (for cardiac and renal patients), HCV viral load, fibrosis stage using Fibroscan (FibroScan®Echosens, Paris, France). Degree of liver fibrosis was categorized into no fibrosis (F0), mild (F0-F1, F1), moderate (F1-2, F2) and marked (F3, F4).

Data related to treatment with oral DAAs were collected: (1) Patients received SOF/LED [either original Harvoni® or the generic form (Ledisbuvir) according to drug availability]. Children aged ^{3} 12 years or weighing ^{3} 35 kg received 400/90 mg SOF/LED as a single tablet once daily orally for 12 weeks. Ledisbuvir was licensed by the Egyptian Ministry of Health in November 2015 after performing a bioequivalence

study *vs* Harvoni® (Gilead Science, Inc, Foster City, California, United States); (2) Data of potential treatment adverse events during treatment course recorded by the caregivers or the examining physicians as: Asthenia, fatigue, headache, jaundice, nausea, vomiting, diarrhea, cough, dyspnea, irritability, insomnia, skin rash, dizziness, arrhythmia, renal dysfunction. The severity categories were mild (does not interfere with daily activity), moderate (interferes with daily activity), severe (necessitates hospitalization), and life-threatening; and (3) Laboratory data of follow up visits at 12 weeks and 24 weeks of therapy: Liver functions and HCV RNA to detect end of treatment response, and SVR respectively. Treatment efficacy was achieved if the patient had SVR (negative HCV RNA 12 weeks after treatment discontinuation).

Patients who received the generic form of SOF/LED (Ledisbuvir) were compared to patients who received the brand form (Harvoni®) regarding demographic data, risk factors for HCV acquisition, degree of hepatic fibrosis, liver functions, SVR and frequency of treatment adverse events.

Statistical analysis

Statistical analysis was performed by SPSS version 21. Continuous variables as age and laboratory results were expressed as mean ± SD (for parametric data) or median with interquartile range (for non-parametric data). Categorical variables as comorbidities, risk factors, treatment response and adverse events were expressed as frequencies and percentage. Group comparisons were performed using Student's *t*-test (for parametric data) or Mann-Whitney *U* test (for non-parametric data) and Pearson χ^2 or Fisher exact test for categorical variables. *P* values < 0.05 were considered statistically significant.

RESULTS

The study included 116 Egyptian children and adolescents with chronic HCV infection whose age ranged between 12-18 years or weighed > 35 kg (even if younger than 12 years). Forty-three patients (37.1%) received the generic form of SOF/LED (Ledisbuvir), while 73 patients (62.9%) received the brand form (Harvoni®). The 8-year-old case in the

Harvoni group who weighed > 35 kg had glycogen storage disease and the 7-year-old case in the Ledisbuvir group who weighed > 35 kg had Down syndrome thus were qualified for treatment.

Patients who received Ledisbuvir were slightly younger than patients who received Harvoni®. Gender was comparable between both groups (Table 1). Regarding the risk factors for HCV acquisition, history of maternal HCV was more frequent in children who received Harvoni®. Meanwhile history of hospitalization and blood products transfusion was more frequent in patients who received Ledisbuvir. Associated comorbidities were significantly more prevalent in children who received Ledisbuvir (Table 1).

Although total bilirubin and international normalized ratio were statistically higher in the Ledisbuvir group, both parameters remained within normal reference ranges and did not signify hepatic dysfunction. Subgroup analyses revealed no impact on SVR or adverse events. Degrees of hepatic fibrosis as assessed by Fibroscan showed comparable results between both groups (Table 2). All patients in both groups achieved end of treatment response and SVR. At end of treatment, patients in the Ledisbuvir group had higher levels of gamma glutamyl transpeptidase, albumin and creatinine (Table 2).

Treatment side effects were mild and transient in all patients and did not necessitate treatment discontinuation in any patient. The most frequently reported side effects were dizziness, fatigue, irritability and headache. The frequencies of different side effects were comparable in both treatment groups except for dizziness which was significantly higher among patients who received Harvoni® (P = 0.003) (Table 3).

DISCUSSION

In recent years, DAAs have provided a realistic prospect for the complete eradication of HCV, particularly when integrated into comprehensive national elimination programs. However, despite the remarkable clinical outcomes associated with DAAs, the high cost of branded formulations such as Harvoni® had previously hindered widespread access,

particularly in resource-limited countries like Egypt, which bears one of the world's highest burdens of HCV[12]. The development and availability of locally manufactured generic formulations have played a pivotal role in addressing this barrier, expanding treatment coverage and reducing the national disease burden[2]. While generic DAAs have shown excellent efficacy and safety outcomes in adult populations in Egypt, data regarding their use in pediatric populations remain limited.

The present study addresses this important knowledge gap by evaluating the safety and efficacy of a generic SOF/LED combination (Ledisbuvir) compared to the branded Harvoni® regimen in a cohort of Egyptian children and adolescents with chronic HCV infection. This study offers valuable real-world data on the performance of these regimens in routine clinical practice by providing evidence from a relatively large cohort of 116 children (from 12-18 years of age or weighting > 35 kg), including 43 treated with the generic formulation and 73 with the branded product. The single-center nature of our study provides consistency in patient management, thereby ensuring standardized treatment protocols and follow-up.

Our study demonstrated that the generic Ledisbuvir achieved comparable SVR rates to those observed with Harvoni® (100%), with both regimens exhibiting excellent virologic response and tolerability profiles with mild, transient adverse effects and no treatment discontinuations. These results align with earlier adult studies from Egypt which showed equivalent efficacy and safety between generic and branded DAAs at a fraction of the cost[4,8]. Studies from similarly resource-limited countries in the Asian-Pacific region reported comparable results in pediatric patients[13]. An Indian study in adolescents with thalassemia major and chronic HCV infection treated with generic SOF/LED similarly reported SVR rates approaching 90%, with no severe adverse events[14]. Our findings were consistent with what was reported in Fouad *et al*[10] study which included 46 HCV infected Egyptian children and revealed comparable SVR (97.8%) with negligible side effects. Reported adverse effects in their study included mild backache, blurring of vision and heartburn.

In children and adolescents, comorbidities such as hematological diseases with iron overload, obesity, cancer, and viral coinfections (HIV and hepatitis B virus) can accelerate the development of hepatic fibrosis[15]. An additional strength of our study is the inclusion of children with comorbid conditions such as treated malignancies, renal and hematological diseases. Although comorbidities were significantly more frequent among our patients who received Ledisbuvir, patients with comorbidities in both groups equally achieved 100% SVR. These findings affirm the safety and efficacy of the affordable generic DAAs in these special pediatric subgroups. This supports the micro-elimination approach advocated by the World Health Organization, targeting high-risk HCV populations such as children with inherited blood disorders, cancer survivors, and those exposed *via* vertical transmission[1,15,16].

Furthermore, our study highlights the role played by the Egyptian government in subsidizing the prices of DAAs, facilitating their widespread availability to both adult and pediatric populations. The financial model adopted by Egypt's national HCV elimination program, where generic formulations are priced at 1%-2% of the original branded drug cost at the producing countries, supports the feasibility and sustainability of such interventions in other low- and middle-income countries[4,12]. This positive experience with generic DAAs in Egyptian children, demonstrates that affordability does not compromise efficacy, and that locally produced treatments can deliver good outcomes equivalent to those of internationally branded medications. The use of the generic formulation of DAAs which is available at approximately 2200 EGP, represents a highly cost-effective alternative to the original Harvoni®, priced at around 9000 EGP, offering comparable efficacy at a substantially reduced financial burden[5].

Recent guidelines from the European Society for Pediatric Gastroenterology, Hepatology and Nutrition recommend the use of pangenotypic DAAs regimens with the shortest feasible treatment durations in children. Notably, the European Medicines Agency recently approved the use of SOF/LED for eight weeks in genotype 1, treatment-naïve, non-cirrhotic children with low baseline viral loads[2]. Shortening treatment duration would improve adherence and reduce costs, particularly in resource

limited contexts. Although our study did not evaluate eight-week regimens, future studies are needed to assess their efficacy in real-world pediatric populations, including those with genotype 4, which predominates in Egypt[17].

Our study has several limitations, including its retrospective design, lack of randomization, and absence of HCV genotyping. Establishing robust pediatric HCV registries is essential to inform national and global policies on diagnosis, care models, and treatment access to achieve WHO's 2030 elimination targets.

CONCLUSION

Our findings provide evidence supporting the use of generic SOF/LED in children with HCV infection. The comparable efficacy and safety outcomes to the branded Harvoni® regimen, coupled with the cost advantages of generics, reinforce their value in national HCV control strategies. Future multicenter studies involving larger pediatric populations and long-term follow-up are warranted to further validate these findings and to support the inclusion of generic DAAs in pediatric treatment guidelines.

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