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Scientific Letter

The Efficacy and Safety of Sofosbuvir-Containing Regimen in the Treatment of HCV Infection in Patients with Haemoglobinopathy

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Infection with HCV is a public health problem and is a leading cause of cirrhosis and liver cancer.[1] HCV infection has been reported in 4.4% to 85.4% of subjects with thalassaemia especially in patients transfused before 1992 when screening of blood donors was still not available. In Duhok city, Iraq, the screening for HCV was only started in 2007 and most of the subjects caught the infection before the screening era. Classically, HCV was treated with Interferon alpha and ribavirin combination.[2] Outstanding development has been made in the treatment of chronic HCV with the development of potent directly acting antivirals (DAAs).[3] These medications may represent a promising approach for the treatment of HCV in patients with haemoglobinopathy. However, the treatment of such cases is challenging because sofosbuvir has not been approved for use in patients under 18 years old and has not been approved in patients with haemoglobinopathy. The aim of this project was to evaluate the efficacy and safety profile of sofosbuvir in the treatment of HCV infection in patients with hemoglobinopathy.

In this study, all patients with haemoglobinopathy (thalassaemia or sickle cell anaemia) and HCV who were referred to the infectious disease unit in Azadi teaching hospital, Duhok, Kurdistan region, Iraq in the period from April 2015 to April 2016 were recruited. In this time, 11 patients visited the unit, ten patients were treated with recombinant interferon (recombinant PEG-IFN-α-2a) at a dose of 180µg/1.73m^2, Ribavirin 14mg/kg body weight and fixed dose of 400mg sofosbuvir for 12 weeks. One patient with cirrhosis was treated with ledipasvir at 90mg administered orally once daily in co-formulation with sofosbuvir 400mg. During treatment, RVR (as defined by undetectable viral load week 4) and as well as post-treatment sustained virologic response (SVR) rates were determined. All patients were followed up by measuring the viral load, ALT and AST levels at four weeks interval. Automated nucleic acid purification was done using the Qiagen QIAsymphony. The Qiagen RT-PCR assay was carried out using the Artus HCV RG-RTPCR Kit and was run on a Rotor-Gene Q thermocycler. The values for the lower limit of detection given by the manufacturer was 34 IU/ml for HCV. HCV genotyping was performed by GEN-C 2.0 reverse hybridization strip assay (Nuclear Laser Medicine, Settala, Mi, Italy). The test discriminates between HCV genotypes on the basis of variations in the 5'-UTR and core regions.

The study protocol was approved by the ethics and research committee of the hospital and the school of Medicine. Written informed consent was obtained from the participants (or their guardians when younger than 18) of this study.

The average age of recruited patients was 16.6±3.2 years, and 7/11 (63.3%) of the subjects were male. 6/11 (54.5%) of the recruited samples were of HCV genotype 4 and 4/11 (36.4%) were of genotype 1. One sample only types as genotype 3. 10/11 (90.9%) of the patients achieved RVR. One patient needed to increase the frequency of blood transfusion, and no significant side effect was reported. 9/11 (81.8%) of the recruited subjects achieved SVR as the viral load was not detected 12 and 24 weeks after stopping treatment (**Table 1**).

In patients with haemoglobinopathy, the standard treatment of HCV included pegylated interferon with or without ribavirin. Recently, new antiviral drugs have been developed for the treatment of HCV infection including the protease inhibitors: NS5A inhibitors, the nucleotide analog NS5B polymerase inhibitor, and the non-nucleotide polymerase inhibitor.[4] These newer drugs are well-tolerated, safer and much more effective

Table 1. HCV infection and treatment characteristics

Gender	Age	Genotype	Viral Load Log	ALT	AST	Albumin	Prior INF	RVR	ETR	SVR	Frequency of Blood transfusion	Side effect
Male	16	4	4.4	49	65	4.2	Yes	Yes	Yes	Yes	same	Body ache
Male	17	1	5.6	69	48	5.2	Yes	No	No	No	same	NA
Male	14	3	6.7	302	336	3.9	Yes	Yes	Yes	Yes	same	Vomiting
Male	15	4	5.2	89	100	4.8	No	Yes	Yes	Yes	same	Body ache
Male	13	4	5.3	123	110	4.0	Yes	Yes	Yes	No	increased	anaemia
Female	14	1	5.6	138	94	4.6	Yes	Yes	Yes	Yes	same	Fever
Female	20	4	6.2	30	47	4.7	Yes	Yes	Yes	Yes	same	Body ache
Female	15	4	6.3	60	58	4.3	Yes	Yes	Yes	Yes	same	Body ache
Male	18	4	5.5	27	15	4.5	No	Yes	Yes	Yes	same	Body ache
Male	16	1	5.9	102	88	4.5	No	Yes	Yes	Yes	same	NA
Female	24	1	5.4	26	25	4.2	Yes	Yes	Yes	Yes	same	NA

Abbreviations: ALT: Alanine transaminase; AST: aspartate aminotransferase; RVR: rapid virologic response; ETR: end of treatment response; INF: interferon; SVR: sustained virologic response

than the previous therapies.[5] However, newer medications are expensive, not available for all patients and not approved for the use in patients with haemoglobinopathy. Worldwide, several studies recruiting thalassaemia patients showed that SVR was achieved in a range of 24% for interferon monotherapy to 51% in patients receiving combined interferon-ribavirin therapy.[6-8] Additionally, the use of standard interferon-containing regimens was fraught with poor tolerability. In our centers, all patients with haemoglobinopathy are candidates for bone marrow transplantation. Infection with HCV is considered contraindication for bone marrow transplantation and hence the eradication of the virus is mandatory. Apart from previous two case reports,[9,10] the first single center experience about the use of sofosbuvir in patients with haemoglobinopathy has been described here. The treatment of our cases was challenging because sofosbuvir has not been approved for use in patients under 18 years old and has not been approved in patients with a haemoglobinopathy. Sustained virologic response was achieved in 81.8% of the patients as the viral load was undetectable 12 and 24 weeks after stopping treatment. Because the sample size was small, it was very hard to evidentiate SVR predictive factors. However, it was noteworthy that the only patient, who did not achieve RVR had a treatment failure, and nine of ten patients, who achieved RVR, also achieved SVR. This study suggests that HCV infection can be successfully treated in patients with haemoglobinopathy. This treatment will hopefully improve the lifestyle of such a group of patients and reduce waiting time for bone marrow operation.

All patients were stable throughout the course of the treatment. Although minor side effects such as body ache and vomiting were observed, none led to complete treatment discontinuation; and an increase in blood transfusion rate was reported in one patient only. Although the combination of sofosbuvir with interferon plus ribavirin was safe and successful in our study, generalized body ache, fever, and anemia that were probably caused by ribavirin and/or interferon affected the quality of life of our patients. Therefore, the combination of sofosbuvir with other DAA such as ledipasvir or daclatasvir would probably be more tolerated with fewer side effects and better quality of life during the treatment course. If such regimens are approved, it would be a breakthrough in the treatment of HCV in subjects with haemoglobinopathy and may prevent HCV-related complication in this group of patients. However, it would be premature to draw reliable conclusions about the optimal regimen, recalling the multitude of new DAAs anticipated in the very near future.

Our study has several limitations. In addition to the retrospective nature of our study, the main limitation is the small sample size used in the report. Therefore, while only minor side effects were reported and the regimen was well tolerated, the number of patients in this study was too small to make claims about the safety of DAAs in such a group of patients. More prospective randomized control trials studies are needed to investigate the efficacy and safety profile of such a regimen.

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