

## Peg-interferon alpha-2a and low-dose ribavirin for treatment of hepatitis C virus infection in patients with sickle-cell anemia in Saudi Arabia

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**BACKGROUND AND OBJECTIVES:** Data regarding the safety and efficacy of antiviral therapy with pegylated interferon (PEG-IFN) and ribavirin (RBV) in patients with sickle-cell disease (SCD) and hepatitis C virus (HCV) infection are scanty. In this study, our aim was to evaluate the safety and efficacy of antiviral therapy with PEG-IFN and low-dose RBV in patients with SCD and chronic HCV infection receiving hydroxyurea in Saudi Arabia.

**DESIGN AND SETTINGS:** This was a prospective interventional study conducted between January 2009 and September 2012 at the outpatient departments of Haematology and Hepatology/Gastroenterology of a tertiary care hospital in Saudi Arabia.

**PATIENTS AND METHODS:** We studied 8 treatment-naive patients (5 males, 63%) with chronic hepatitis C and SCD receiving hydroxyurea who were treated with PEG-IFN alpha-2a (180 µg weekly) and low-dose RBV (200 mg daily). Early virological response (EVR) and sustained virological response (SVR) rates were assessed in all patients.

**RESULTS:** All patients were infected with HCV genotype 1 (n=6.8%) or 4 (n=22%). EVR was obtained in 3 patients (38%) and SVR in 6 patients (7%). During the study, there was no increase in the number of blood units transfused and emergency visits due to painful crises.

**CONCLUSION:** In Saudi Arabian patients with SCD and chronic HCV infection on hydroxyurea, PEG-IFN and low-dose RBV treatment proved to be efficacious and safe.

Sickle-cell disease (SCD), one of the commonest hemoglobinopathy worldwide, is an autosomal recessive disorder caused by point mutation forming an abnormal hemoglobin S (HbS). It may lead to complications such as vaso-occlusive crises, acute chest syndrome, infections, strokes, renal failure, gallstones, and acute exacerbation of anemia from splenic sequestration and/or aplastic, hyperhemolytic, and megaloblastic crises.<sup>1,2</sup>

Approximately 8% of African Americans carry the sickle-cell gene (i.e., sickle-cell trait), while the homozygous state causing sickle-cell anemia (SCA) is present in approximately 0.15% of African Americans.<sup>3</sup> SCD is common in Saudi Arabia with a reported sickle-cell trait frequency of around 25% in one of the provinces and SCA incidence being up to 2%.<sup>4,5</sup> Many

complications of SCA require treatment in the form of blood transfusions (simple or exchange), which carry the risk of blood-borne infections, and an estimated 10% of adults with SCD is hepatitis C-virus (HCV) positive.<sup>6</sup>

The exact prevalence of HCV infection in patients with SCA in Saudi Arabia is not fully known although the average annual incidence of seropositivity for HCV per 100 000 population is 78.4, while another study from the central region of Saudi Arabia reports a prevalence of 18.2% among SCD patients.<sup>7,8</sup> Despite encouraging results in the treatment of chronic hepatitis C using a combination of pegylated interferon (PEG-IFN) and ribavirin (RBV), patients with SCA and having a chronic HCV infection have seldom been considered suitable for such treatment because of the

risk of RBV-induced hemolysis that might aggravate pre-existing anemia.<sup>9,10</sup> A few publications recently reported the use of a combination therapy in these patients with a considerable success despite some side effects, although due to a small number of patients in some studies and the lack of prospective analysis in another makes them fall short to make a generalized recommendation.<sup>11-14</sup> Furthermore, the use of hydroxyurea—which over the last decade was used in SCA patients to determine reduction in acute painful episodes and acute chest syndrome events, and to raise fetal hemoglobin levels—was not specifically assessed in any of the studies.<sup>11-14</sup>

In this study, our aim was to assess the efficacy and safety of a combination therapy of PEG-IFN and low-dose RBV (i.e., 200 mg daily with a gradual increase up to 200 mg twice daily) to treat patients with SCA and HCV infections and taking at least 500 mg daily of hydroxyurea in a tertiary care hospital setting in Saudi Arabia.

## PATIENTS AND METHODS

This was a prospective interventional study conducted between January 2009 and September 2012 at the outpatient departments of Haematology and Hepatology/Gastroenterology of a tertiary care hospital in Saudi Arabia.

This study included patients with SCA diagnosis based on history, examination, and hemoglobin electrophoresis who have had at least 1 transfusion (simple or exchange) in the past, on at least 500 mg daily of hydroxyurea, who had positive HCV antibodies on third-generation enzyme-linked immunosorbent assay testing and detectable serum HCV-RNA on polymerase chain reaction assay, and who were consistently followed at our departments. Patients were excluded if they had a coinfection with human immunodeficiency virus, hepatitis B virus, or schistosoma; or if they suffered from autoimmune hepatitis, and/or if they showed other liver diseases like iron overload or primary biliary cirrhosis or presence of liver lesion or cirrhosis on ultrasound; or if the patient records were incomplete. Therefore, a total of 8 patients who were of Saudi nationality were selected using the above-mentioned selection criteria.

We collected demographic data (age, gender) and clinical data (transfusion requirement in the year before and during the study; emergency room admissions for painful crisis in the year before and during the study), serum alanine aminotransferase, and hemoglobin levels. Serum HCV-RNA levels (expressed as IU/mL) and HCV genotype were assessed in all patients

before treatment. Serum HCV-RNA was subsequently performed at the following intervals: (1) at week 12 to assess an early virological response (EVR)—defined as 2 log decrease in HCV RNA copies from baseline or HCV-RNA negativity (complete EVR, cEVR), (2) at weeks 24 and 48 to assess the end-of-treatment response for genotypes 2/3 and 1/4, respectively, (3) and 24 weeks after the completion of treatment to assess a sustained virological response (SVR) to therapy.<sup>15</sup>

All our patients were treated with PEG-IFN pegylated interferon alpha-2a (Pegasys, Roche) 180 µg subcutaneously weekly. RBV (Copegus, Roche) 200 mg tablets were used initially once daily for 1 week and then increased to 200 mg tablets twice daily.

The ethical approval of the study was given by the research and ethics committee of the Institution.

## RESULTS

Eight treatment-naive patients (5 males, 63%) with SCA and having a chronic HCV infection were treated with PEG-IFN and low-dose RBV. The patients' main characteristics are shown in **Table 1**. None of the patients had clinical signs suggestive of liver cirrhosis. Two patients (25%) had a low pretreatment viral load (i.e.,  $<8.0 \times 10^5$  IU/mL), and HCV genotype was 1 in 2 patients (25%) and 4 in 6 patients (75%). As none of the patients was infected with HCV genotype 2 or 3, the programmed duration of antiviral treatment was 48 weeks in all patients.

The median number of transfusion units received in the year preceding the study was 2 (range, 0-4 units), and the median number of emergency visits for painful crises in the year before treatment was 2 (range, 0-5 visits).

Antiviral therapy was well tolerated, and none of the patients withdrew from treatment. A step-wise increase in the RBV dose was tolerated by all patients. None of the patients had a cEVR, and 3 patients had an EVR (38.0%). An ETR was observed in 6 patients (75%) and an SVR was obtained in 6 patients (75%). Both patients who did not obtain an SVR were infected with HCV genotype 4 and had not obtained an EVR (**Figure 1**). During antiviral therapy, the median number of units transfused was 1 (range, 0-6 units) and the median number of visits due to painful crises was 1 (range, 0-6 visits).

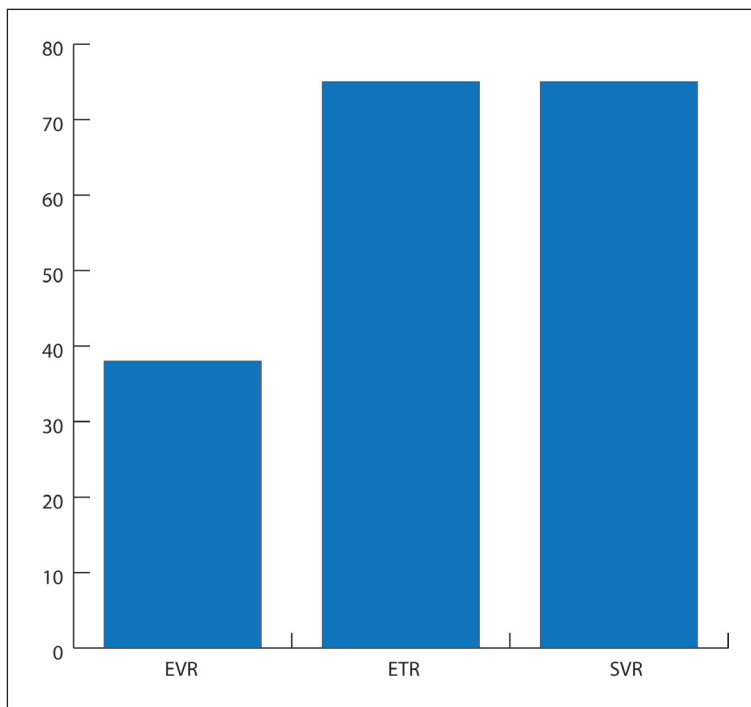
## DISCUSSION

HCV is a common blood-borne infection worldwide, and around 8% of patients with SCA are infected with HCV.<sup>6</sup> Untreated chronic HCV may progress to liver cirrhosis and hepatocellular carcinoma.<sup>16</sup> Over the last

**Table 1.** Baseline demographic, biochemical, and virological characteristics of the study patients.

Variable	Unit	Median	Range
Age	yr	30	21-45
ALT	IU/mL	47	20-146
Hemoglobin	g/dL	10.0	8.1-11.0
HCV RNA	IU/mL	$1.8 \times 10^6$	$3.1 \times 10^4$ - $21.2 \times 10^6$

ALT, alanine aminotransferase, HCV: hepatitis C virus.



**Figure 1.** Virological response rates obtained in the study (EVR, early virological response; ETR, end-of-treatment response; SVR, sustained virological response).

decade, due to the use of hydroxyurea and improved care, SCA patients are living longer and thus treatment of chronic HCV infection to prevent long-term liver complications is becoming a priority.<sup>3,17</sup> The use of a combination therapy in patients with hemoglobinopathies was traditionally thought to be hazardous because of secondary iron overload and concerns related to RBV-induced hemolysis. However, the poor results for SVR to PEG-IFN monotherapy have led to the studies of PEG-IFN and RBV combined treatment also in patients with SCA.<sup>13,14</sup>

In this study we observed that HCV patients with SCA on hydroxyurea can be treated with a PEG-IFN low-dose RBV without relevant side effects. In particular, the antiviral therapy was not associated with

an increase in the number of blood units transfused and the number of emergency visits due to painful crises during treatment. None of the patients withdrew from treatment. Antiviral therapy obtained an SVR of 75% in treatment-naïve patients with genotypes 1 and 4 with no relapse, although it should be taken into account that patients were prevalently young, viral load was low (i.e.,  $<8.0 \times 10^5$  IU/mL) in 25% of the patients, and genotype 1 patients represented a minority of treated patients (25%) though none of them had a low viral load. These findings are in keeping with epidemiology of HCV in Saudi Arabia, showing that the predominant genotype in our geographical area is genotype 4, followed by genotype 1, in whom standard treatment of a combination of PEG-IFN and RBV for 48 weeks is effective in up to 44% to 54% of patients with genotype 1, and 58% to 86% of patients with genotype 4.<sup>7,8,15</sup> Nevertheless, our study was limited by the small sample size and by the fact that no patients with HCV genotypes 2 and 3 were enrolled.

Our results compare favorably with previous results obtained in similar cohorts. Swaim et al. reported successful treatment of 2 patients with SCA and HCV using interferon alpha-2b and RBV for the first time in 2000.<sup>11</sup> Ancel et al reported some success in 5 patients with SCA and HCV albeit a slight increase in transfusion was required for the group of patients with thalassemia alone.<sup>12</sup> Ayyub et al also described 8 patients with SCA and HCV who were treated with PEG-IFN alpha-2a and RBV for 1 year obtaining 63% SVR rate.<sup>13</sup> In another study that included retrospectively analyzed 52 patients with SCA and HCV who were treated with standard PEG-IFN and full-dose RBV full dose, Issa obtained 71.2% SVR rate without any major side effects.<sup>14</sup> As hydroxyurea reportedly suppresses HCV replication in humans, we cannot exclude that the good SVR rate we observed in this study might have been due also to hydroxyurea coprescription, although this hypothesis is merely speculative.<sup>17-19</sup>

This study undoubtedly has some drawbacks such as lack of interleukin-28B (IL-28B) polymorphisms assessment, and lack of histological characterization of patients. As these 2 important pretreatment determinants of response to antiviral therapy were missing in our population, we cannot exclude that the good SVR we obtained might have been due to favorable IL-28B polymorphisms and mild histological stage.<sup>20,21</sup>

To conclude, our study showed that the treatment of HCV infection in patients with SCA in Saudi Arabia with standard PEG-IFN and low-dose RBV was well-tolerated, and we obtained a satisfactorily

SVR rate. Future prospective similar multicenter studies from the region are needed to confirm these results to further recommend this sort of treatment regimen so as to eliminate the burden of HCV infection among patients with SCA without subjecting them to additional complications and side effects.

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