Successful treatment of chronic hepatitis C virus infection with peginterferon alpha-2a and ribavirin in patients with sickle cell disease

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ABSTRACT

الغرض من دراسة هذه السلسلة من المرضى هو تقييم مدى فاعلية وأمان استخدام دمج عقاري الريبافيرين مع البجيلاتد انترفيرون (alpha–2a) في مرضى داء الخلايا المنجلية (SCD) المصابين بالالتهاب الكبد الفيروسي (HCV). وقد شملت هذه الدراسة ثمانية من المرضى المترددين على مستشفى الملك عبد العزيز ومركز الأورام – جدة – المملكة العربية السعودية، خلال الفترة مابين عام 2003م وحتى عام 2006م. تمت متابعة جميع المرضى المصابين الكبد الفيروسي (HCV)، حيث تم إعطاؤهم عقار الريبافيرين مع البجيلاتد انترفيرون (alpha–2a) طوال لمدة عام. أظهرت العدوى الفيروسية لدى جميع المرضى الثمانية ودون استثناء استجابة مبكرة كاملة للعلاج. استمرت مظاهر تلك الاستجابة حتى نهاية فترة العلاج عند سبعة من المرضى حيث لم يعاود الحمض النووي للفيروس (HCV RNA) للظهور في الدم عند أي منهم طوال تلك الفترة. كما أنه قد تحقق أيضا استمرار الاستجابة لأكثر من ستة أشهر بعد توقف العلاج عند خمسة من المرضى. تم قياس تركيز الهيموجلوبين في دم المرضى قبل بدأ العلاج، ثم بعد البدء بشهر، ثلاثة أشهر، ستة أشهر، تسعة أشهر واثني عشر شهراً. لم يكن هناك أي تغيير كبير أو هام في تركيز الهيموجلوبين طوال فترة العلاج. لذا فانه يمكننا القول، بان علاج الالتهاب الكبدي الفيروسي(HCV) لدى مرضى داء الخلايا المتجلية (SCD) باستخدام البجيلاتد انترفيرون (alpha–2a) مع عقار الريبافيرين يبدو فعال وآمن.

The objective of this case series was to determine the efficacy and safety of combined treatment with ribavirin and peginterferon alpha-2a in sickle cell disease (SCD) patients with chronic hepatitis C virus (HCV) hepatitis. Eight patients in King Abdulaziz Hospital & Oncology Center, Jeddah, Kingdom of Saudi Arabia from 2003 and 2006 with chronic HCV infection were treated with peginterferon alpha-2a and ribavirin for one year. All 8 patients had a complete early virological response. Seven out of 8 had an end of treatment response with undetectable HCV RNA at the end of therapy, 5 of whom also maintained a sustained virological response when assessed 6 months after the end of treatment. Hemoglobin concentrations measured at one, 3, 6, 9, and 12 months of treatment showed no significant changes from that measured as baseline. Treatment of chronic HCV hepatitis in patients with SCD with peginterferon alpha-2a and ribavirin seems safe and effective.

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Patients with sickle cell disease (SCD) can develop hepatic insults for various reasons, including repeated hepatic infarctions, hemosiderosis due to repeated blood transfusions, cholelithiasis, and transfusion related B and C hepatitis.[1] In many instances, hepatic dysfunction is multi-factorial.[2] Sickle cell disease patients are currently living longer due to the improved management of complications of this debilitating disease.[3] As a result, SCD patients with hepatitis C virus hepatitis are more likely to develop liver cirrhosis, if the appropriate treatment of HCV is not offered in time. Recently, considerable progress has been made in the treatment of chronic hepatitis C. The current gold standard for treatment involves the combined use of peginterferon and ribavirin. This form of treatment has been able to achieve a sustained virological response (SVR) in up to 60% of patients with genotype 1 and 4, and up to 90% in those with genotype 2 and 3.[4] However, patients with SCD and those with other hemoglobinopathies are usually considered to be unsuitable for this treatment,

as it is believed that ribavirin induced hemolysis can further aggravate anemia.[5] The objective of this case series was to determine the efficacy and safety of combined treatment with ribavirin and peginterferon alpha-2a in SCD patients with chronic HCV hepatitis.

Case Report. All confirmed SCD patients attending the medical and hematology clinics of King Abdulaziz Hospital and Oncology Center, Jeddah, Kingdom of Saudi Arabia from 2003 to 2006 were screened for HCV serology using a third generation ELISA test. Eight patients were identified with confirmed diagnosis of SCD, and positive serology for hepatitis C. All these patients had a quantitative analysis of HCV PCR (Amplicor HCV, Roche, Basel, Switzerland) carried out in Jeddah Regional Laboratory, showing significantly elevated viral load. 2. The patients were followed up for a period of at least six months before starting treatment and confirmed to have persistently elevated HCV RNA during the pre-treatment follow up period. None of the patients had previous history of strokes, epilepsy, psychiatric disorders, positive HIV serology or liver cirrhosis. Informed consent for the treatment was sought from all 8 patients, or from their guardians, Ethical approval letter was obtained from the Ethical Committee of King Abdulaziz Hospital, Jeddah. Patients had a baseline assessment of complete blood count (CBC), hemoglobin electrophoresis, coagulation profile, chemical profile including full liver function tests, thyroid function tests, serological screening for hepatitis B virus (HBV), HIV, and alpha fetoprotein. The HCV genotype was determined in all patients. An abdominal ultrasound was carried out in every patient. Liver biopsy was performed in patients who agreed to undergo the procedure. Histological activity was graded and staged according to the Ishak modified histological activity index (HAI).[6] Patients with no consent for liver biopsy were also considered for treatment if there was no clinical evidence of liver cirrhosis. Treatment was started with a standard dose of peginterferon alpha-2a (Pegasys 180 micrograms pre-filled syringes, Roche) 180 micrograms subcutaneously, once per week and ribavirin (Rebetol 200 capsules, Schering-plough, Kenilworth, New Jersey) 200 mg twice daily. The ribavirin dose was gradually increased to 400 mg twice daily over a period of 4-8 weeks. Patients were asked to continue their usual treatment with folic acid (5 mg daily) and hydroxyurea (500 mg twice daily). Treatment was continued for one year during which patients were seen at 2-week intervals for the first 2 months, and monthly thereafter. During each visit, patients had a complete assessment including CBC and liver function tests carried out. The HCV PCR and thyroid profile was repeated at 3, 6, and 12 months after the start of treatment, and 6 months after the end of the treatment. Complete early virological response (cEVR) was demonstrated by the absence of HCV RNA during the quantitative analysis of HCV PCR 12 weeks after the start of treatment. End of treatment response (ETR) and sustained viral response (SVR) were defined by an undetectable HCV RNA immediately and 26 weeks (6 months) after the end of treatment. The patient characteristics at baseline are summarized in **Table 1.** All patients were Saudi nationals and all were confirmed to have SCD by hemoglobin electrophoresis. Patient ages ranged from 18-30 years with a mean age of 24.63±4.5 years. The male to female ratio was 5:3. The concentrations of hemoglobin S ranged from 57-89%, with a mean percentage of 80.29±10.9. Hemoglobin A, in studied patients ranged from 2.5-26.7%, with a mean percentage of 9.19±7.55,

Table 1 - Baseline characteristics of patients with SCD and HCV hepatitis.

Patient serial number	Age (in years)	Gender	Weight (Kg)	Hematological diagnosis (HB SS)			ALT (U/ml)	HCV PCR (U/ml)	HCV genotype	Liver histology (Ishaq HAI)		Comorbid conditions
				HBS %	HBA %	HBF %				Grade score	Stage	
1	24	Male	42	78	9.8	8.2	83	480,000	1	10	1	Nil
2	20	Male	52	87	6.5	6.5	17	66,300	4	8	2	Nil
3	18	Male	45	57.8	26.7	12.2	60	649,000	4	8	2	HBV hepatitis
4	25	Male	44	77	9	14	50	200,000	4	Not done		History of ADEM
5	30	Male	41	92.5	2.5	5	45	692,000	4	6	2	Nil
6	30	Female	38	89	3.5	6.5	44	708,000	4	Not done		Nil
7	28	Female	39	85	6.5	8.5	46	524,000	1	10	1	Nil
8	22	Female	41	76	9	15	45	350,000	1	6	2	Nil
Mean +/- SD	24.63 ± 4.5		42.75 ± 4.4	80.29 ± 10.9	9.19 ± 7.55	9.49 ± 3.76	48.75 ± 18.36	458662.5 ± 236.11				

SCD - sickle cell disease, HCV - hepatitis C virus, HBV - hepatitis B virus, HB - hemoglobin, ALT - alanine aminotransferase, PCR - polymerase chain reaction, HAI - histological activity index, ADEM - acute disseminated encephalomyelitis.

Table 2 - Response of HCV hepatitis to anti-viral treatment.

Patient serial number	Anti-viral treatment	Duration in months	cEVR	ETR	SVR
1	Peg interferon alpha-2a, Ribavirin	12	Present	Present	Present
2	Peg interferon alpha-2a, Ribavirin	12	Present	Present	Present
3	Peg interferon alpha-2a, Ribavirin	12	Present	Present	Present
4	Peg interferon alpha-2a, Ribavirin	12	Present	Present	Present
5	Peg interferon alpha-2a, Ribavirin	12	Present	Present	Absent
6	Peg interferon alpha-2a, Ribavirin	12	Present	Absent	Absent
7	Peg interferon alpha-2a, Ribavirin	12	Present	Present	Present
8	Peg interferon alpha-2a, Ribavirin	12	Present	Present	Absent

HCV - hepatitis C virus, cEVR - complete early virological response, ETR - end of treatment response, SVR - sustained virological response

Table 3 - Changes in hemoglobin concentration, WBC, and platelet counts during the course of treatment.

Hematologic parameter	Follow up time in months after start of therapy					
	At baseline	One	Three	Six	Nine	Twelve
Hemoglobin concentration in g/dl						
Mean	9.63	9.7	9.53	9.6	9.6	9.88
SD	1.0	0.78	0.58	0.58	0.52	0.94
Range	8.5-11.0	8.9-11.0	8.9-10.4	8.8-10.2	9.0-10.0	8.5-11.3
Median	9.4	9.4	9.55	9.8	9.7	10.05
WBC count X 10^3 /µl						
Mean	9.67	8.05*	7.93*	7.06*	7.21*	7.58
SD	2.3	2.3	2.48	2.06	2.21	2.23
Range	6.1-12.3	4.5-10.7	3.7-11.3	2.9-9.5	3.3-9.8	4.1-10.7
Median	10.3	8.65	8.1	7.15	7.6	7.75
Platelet count X 10^3 /µl						
Mean	417	310.3	380	274.5*	274.8*	290*
SD	141	104.2	86.1	110.6	119.74	133.3
Range	198-579	154-460	128-380	78-410	67-432	84-472
Median	423	329.5	304.5	317	259.5	267.5

WBC - white blood count, *significantly different from the corresponding baseline value (p<0.05 - please provide exact values for all significant results)

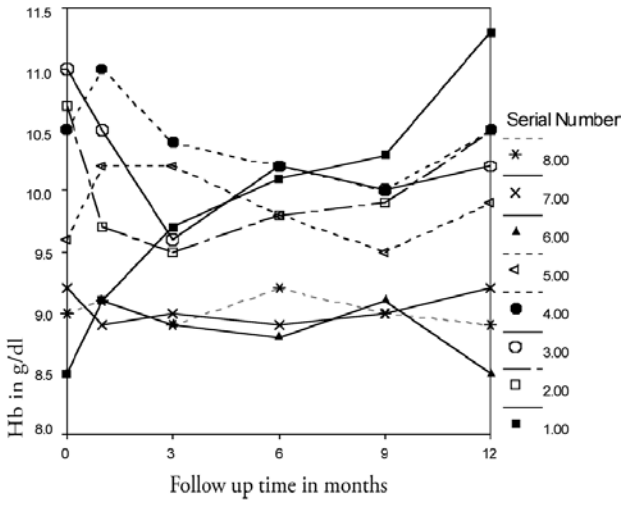

Figure 1 - Hemoglobin concentrations of individual patients during the course of treatment.

while hemoglobin F ranged from 5-15%, with a mean percentage of 9.49±3.76. Five patients had genotype 4, while the other 3 had genotype 1. Pre-treatment quantitative HCV PCR varied from 66,300 IU/ml to 708,000 IU/ml with a mean value of 458,662.5±236. One patient had an alanine aminotransferase (ALT) of 17 units/ml, while all the other patients had elevated ALT levels with reference to local laboratory values. One patient had both HCV and HBV hepatitis. It was decided that HCV hepatitis would be treated in the first phase of his therapy. Another patient had a history of acute disseminated encephalomyelitis 4 years before the study. He was left with a residual non-progressive neurological deficit. Liver biopsy was performed in 6 patients, while 2 refused to give consent for this. Using Ishak's modified HIA score, the necro-inflammatory index varied from 6-10 with a median score of 8. Staging score varied from 1-2 in all patients who underwent liver

biopsy. The responses of patients to anti-viral therapy are shown in **Table 2.** All patients were able to complete therapy for one year. All patients achieved a cEVR as shown by the absence of HCV RNA 3 months after the treatment. Only one female patient with genotype 4 did not have ETR, with an HCV PCR of 480,000 IU/ml at the end of treatment. Five patients (62.5%) maintained an SVR at 6 months after the end of treatment. Three patients were unable to achieve SVR and had significant HCV viral burdens during quantitative HCV RNA estimation. Two of those patients had genotype 4, while one had genotype 1. Side effects of treatment mainly consisted of headaches, generalized body aches, fever, and anorexia. No significant hematological events like anemia or leukopenia were encountered during the course of treatment. None of the patients required blood transfusion and/or discontinuation of therapy due to the side effects. **Table 3** summarizes the changes in hemoglobin concentration, WBC count, and platelet count for all the patients during the course of treatment. **Figure 1** shows tracings of hemoglobin concentrations of individual patients. At baseline, hemoglobin level ranged from 8.5-11.0 g/dl, with a mean of 9.63±1.0 and a median of 9.4 g/dl. No significant changes were observed in the hemoglobin concentration of patients at any stage of treatment. The hemoglobin concentration at the end of treatment ranged from 8.5-11.3 with a mean of 9.88±0.94 and a median of 10.05 g/dl. There was no statistically significant difference from the corresponding baseline value. Although the mean platelet count was significantly decreased starting one month after therapy, no clinical intervention or treatment discontinuation was necessary in any of the patients.

Discussion. The current case series focuses on the treatment of HCV in patients with SCD in an open label form. All the patients were known to have SCD and were already receiving treatment with hydroxyurea. All the patients had either genotype 1 or 4, and thus belonged to the 'difficult to treat' group of patients. In our series, an SVR of approximately 62% was observed, which is comparable to patients without SCD and infected with similar genotypes.[4] The medical literature contains very few reports on the treatment of HCV in hemoglobinopathy patients in general and in those with SCD in particular. In 2000, Swaim et al[7] reported the successful use of interferon alpha-2b and ribavirin for the treatment of HCV infection in 2 patients known to have SCD. They mentioned an ETR in one patient and a cEVR in the other, but no comment was made on the SVR. In 2002, Li et al[8] described their experience of treating HCV in a group of thalassemic patients with interferon alpha-2b and ribavirin. They reported an SVR of 72.2%. Nonetheless, the transfusion requirements were increased by 30% during the treatment period. Hamidah et al[9] also reported successful treatment with peginterferon alpha-2b and ribavirin in a thalassemic patient with chronic hepatitis C who was a non-responder to standard interferon-based therapy. Again, transfusion requirements were significantly increased in thalassemic patients during combination therapy due to ribavirin-induced hemolysis. More recently, an abstract presented by Ancel in The Digestive Disease Week in May 2006, described the treatment of chronic hepatitis C in 5 thalassemia and 5 SCD patients with interferon alpha-2b and ribavirin.[10] Eighty percent of those patients had genotypes 1 and 4 yet they were able to achieve an SVR of 60%. Only patients with thalassemia required increased blood transfusion whereas none of those with SCD required transfusion during or after treatment.

Reluctance to use ribavirin in patients with hemoglobinopathies is based on the drug's ability to cause or to aggravate anemia by causing hemolysis.[4] In the present study, however, no hematological problems were observed in any of the treated patients. None of the patients required discontinuation of therapy and none of them received any blood transfusions during the course of therapy. Some approaches have been suggested in the literature to avoid potential hematological problems of ribavirin, one of which is to start and maintain the patients on hydroxyurea before giving ribavirin. Through its ability to increase hemoglobin F, hydroxyurea may decrease the chances of hemolysis and anemia.[3] In our patients, all of the patients were already on treatment with hydroxyurea and had elevated concentrations of hemoglobin F as evident from their pre-treatment hemoglobin electrophoresis. Whether hydroxyurea contributed to the prevention of any hemolysis is not clear. Another approach adopted by Ancel[10] to avoid ribavirin-induced hematological complications, is to give a reduced dose of ribavirin. In our patients, therapy was started at a lower dose of ribavirin (200 mg twice daily), but the full 400 mg twice-daily dose could be reached within 4-8 weeks of therapy initiation. The absence of any ribavirin-induced hemolysis in this study raises an important question: Are all patients with different types of hemoglobinopathies equally susceptible to ribavirin-induced hemolysis? It is worthwhile to note that in all previous literature reports on HCV treatment in hemoglobinopathy patients, only patients with thalassemias had an increase in transfusion requirements.[10] This underscores the importance of conducting sufficiently larger studies to unravel the fine differences in response to treatment in the various subsets of hemoglobinopathic patients. It is important to note that all our patients had relatively low viral load. The reason for this is not obvious. It is well established that patients with high viral load negatively predict the response to treatment.[11] Good clinical response seen in

our series may be attributed to the low viral load of our patients.

Our study describes the successful use of combined pegylated interferon alpha-2a and ribavirin for the treatment of a group of pure SCD patients with chronic HCV hepatitis of genotypes 1 and 4. In conclusion, this report encourages the combined use of peginterferon and ribavirin based anti-viral therapy in SCD patients with chronic HCV hepatitis. The therapy seems to be effective with viral responses comparable to those of non-SCD patients, and also appears to be safe with no reported increase in hematological problems. Further studies on larger populations in a randomized controlled setting are required to provide stronger evidence of safety and efficacy of this therapy in chronic C virus hepatitis in patients with SCD.

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