World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/1948-5182office
wjh@wjgnet.com
doi:10.4254/wjh.v2.i5.180

World J Hepatol 2010 May 27; 2(5): 180-184
ISSN 1948-5182 (online)

BRIEF ARTICLE

Safety of pegylated interferon and ribavirin therapy for chronic hepatitis C in patients with sickle cell anemia

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Received: January 16, 2010 Revised: May 6, 2010
Accepted: May 13, 2010
Published online: May 27, 2010

Abstract

AIM: To evaluate the safety and efficacy of combined pegylated interferon and ribavirin for the treatment of chronic hepatitis C (HCV) in patients with sickle cell anemia (SCA).

METHODS: Fifty-two patients with SCA and HCV were treated over a period of 7 years from June 2002 to July 2009. Their medical records were reviewed for: age at treatment, sex, body mass index, Hb level at the start of therapy and on follow-up, hemoglobin electrophoresis, liver function tests, G6PD level, LDH, bilirubin, HCV-RNA viral load, HCV genotype, liver biopsy, duration of treatment, and side effects. All were treated with pegylated interferon and a standard dose of ribavirin. The treatment was continued for 24 wk for those with genotype 2 and 3 and for 48 wk for those with genotype 1 and 4.

RESULTS: Fifty-two patients (30 females and 22 males) were treated. Their mean age was 29.5 years (range 15-54 years). HCV genotype was determined in 48 and 15 had liver biopsy. Their mean pre-treatment HCV-RNA viral load was 986330 IU/mL (range 12762-3329282 IU/mL). The liver biopsy showed grade Ⅰ in 6 and grade Ⅱ in 9 and stage Ⅰ in 13 and stage Ⅱ in 2. Only 8 were receiving hydroxyurea at the time of treatment. All tolerated the treatment well and none experienced a decrease in their Hb which required blood transfusion pre, during or after therapy. There were no hematological side effects attributable to ribavirin at the usual recommended dose. Thirty-seven (71.2%) achieved SVR at 6 mo after the end of treatment. The remaining 15 were non-responders. Two of them showed an ETR but had a relapse. The remaining 13 had a relatively significant HCV-RNA viral load with a mean HCV-RNA viral load of 1829741.2 IU/mL (900000-3329282 IU/mL) and eight of them had HCV genotype 1, four had HCV genotype 4, and one had HCV genotype 5.

CONCLUSION: Patients with SCA and HCV can be treated with pegylated interferon and ribavirin at the usual recommended dose. This is even so in those who are not receiving hydroxyurea. The treatment is safe and effective and the response rate is comparable to those without SCA.

Key words: Sickle cell anemia; Chronic hepatitis C; Treatment

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Issa H. Safety of pegylated interferon and ribavirin therapy for chronic hepatitis C in patients with sickle cell anemia. *World J Hepatol* 2010; 2(5): 180-184 Available from: URL: http://www.wjgnet.com/1948-5182/full/v2/i5/180.htm DOI: http://dx.doi.org/10.4254/wjh.v2.i5.180

INTRODUCTION

Sickle cell anemia (SCA) is one of the common hemo-

globinopathies in the world. In the Eastern Province of Saudi Arabia, SCA is common with a reported sickle cell trait frequency up to 25% and a sickle cell anemia frequency of about 2%[1,2]. It is well known that SCA can affect any part of the body and one of the common organs to be affected is the hepatobiliary system. This can manifest in several different ways including cholelithiasis, choledocholithiasis, hepatic crisis, hepatic sequestration and cholestatic jaundice as well as transfusion related hepatitis B and C[3-8]. The exact frequency of hepatitis B and C in patients with SCA in Saudi Arabia is not known but the average annual incidence of seropositivity per 100 000 population was 104.6 for HBV and 78.4 for HCV[9]. An 18.2% prevalence of antibodies to HCV was reported among sickle cell patients in the Central region of Saudi Arabia[10]. The life expectancy of patients with SCA has improved considerably, attributable to better understanding of the disease, improved medical and surgical management and the use of hydroxyurea[11-13]. However, this will put SCA patients with chronic hepatitis B and C at risk of developing liver cirrhosis, hepatocellular carcinoma and liver failure if their hepatitis B and C are not treated. In spite of the markedly improved results in the treatment of chronic hepatitis C using the combined therapy of pegylated interferon and ribavirin, patients with SCA and chronic hepatitis C have not been considered suitable for such treatment because of the believed risk that ribavirin will induce hemolysis and severe anemia which can aggravate their already existing anemia[14-16]. Recently however there have been three publications reporting success of such treatment in patients with SCA and HCV C although the number of patients reported was small[17-20]. This report describes our experience in the management of 52 SCA patients with HCV using pegylated interferon and ribavirin at the usual recommended dose.

MATERIALS AND METHODS

In June 2002, we started treating SCA patients with HCV using pegylated interferon and ribavirin at Qatif Central Hospital, Saudi Arabia. This was approved by the ethical and research committee and an informed written consent was obtained from each patient explaining the type and duration of treatment as well as the possible side effects. This was a retrospective study and the following information was noted: age at treatment, sex, body mass index, Hb level at the start of treatment and on follow-up, hemoglobin electrophoresis, liver function tests, G6PD level, LDH, bilirubin, HCV-RNA viral load, HCV genotype, liver biopsy, duration of treatment, and side effects. HCV serology screening was done using a third generation ELISA test and confirmatory RIBA test. HCV-RNA was detected and assayed using an automated extraction system (Cobas Ampliprep). HCV Quantification and Detection was performed using Abbott Real Time M2000 RT instrument and the COBAS TaqMan HCV Test (RT-PCR technology) on the COBAS AmliPrep system (Roche) These assays detect and quantitate genotypes (1-6). An Internal Control is included in the assays to monitor any possible amplification inhibitors.

Prior to treatment, all patients had complete blood count, liver function tests, thyroid function tests, alpha fetoprotein, autoimmune profile, HBV and HIV screening and an abdominal ultrasound as part of their work-up. None of our patients had co-infection with HIV or HBV. The Hb level, LDH and bilirubin levels were monitored and checked initially, and during follow-up at 2 wk, 4 wk, 8 wk, 12 wk, 16 wk, 24 wk, 32 wk, 40 wk and 48 wk. The METAVIR fibrosis grading scale was used to grade and stage liver fibrosis[21]. Treatment was initiated within two to three weeks post liver biopsy. Only 48 out of 52 patients were HCV genotyped as this facility was not available in our hospital at the beginning of the study. All our patients were treated with pegylated interferon alpha-2a (Pegasys 180 micrograms pre-filled syringes, Roche) 180 microgram subcutaneously, once per week or pegylated interferon alpha-2b (Peginterone, Schering-plough) 1 ug/kg subcutaneously, once per week and ribavirin. Ribavirin Rebetol (200 mg capsules, Schering-Plough) or Copegus 200 mg tablets, Roche) was used in a dose of 400 mg twice daily for those with HCV genotype 2 and 3 as well as those in whom HCV genotype was not known and 600 mg twice daily for those with HCV genotype 1, 4 and 5. The treatment was continued for 24 wk for those with genotype 2, 3 and those in whom HCV genotype was not known and for 48 wk for those with genotype 1, 4 and 5. Early virological response (EVR), end of treatment response (ETR) and sustained viral response (SVR) were documented when HCV RNA was undetectable or < 2 log, in comparison with baseline viral load at 12 wk from treatment (EVR), undetectable HCV-RNA at the end of treatment (ETR) and at 6 mo following completion of treatment respectively (SVR).

RESULTS

Fifty-two patients with SCA and HCV (Table 1) were treated, comprising 30 females and 22 males. Their mean age at the time of treatment was 29.5 years (range 15-54 years). Their mean HbS was 74.4% (66%-89%) and their mean HbF was 22.5% (9.6%-33.6%). Twelve (23.1%) had G6PD deficiency. HCV genotype was done in only 48. This indicated genotype 2 in 20; genotype 1 in 13, genotype 4 in 8, genotype 3 in 6 and one had genotype 5. Their mean pretreatment quantitative HCV- RNA level was 986330 IU/mL (range 12762-3329282 IU/mL). Fifteen underwent liver biopsy. This showed grade Ⅰ in 6 and grade Ⅱ in 9 and stage Ⅰ in 13 and stage Ⅱ in 2. Only 8 were receiving hydroxyurea at the time of treatment. All patients completed their therapy and in none of them was the treatment reduced or discontinued because of major side effects, hemolysis or bone marrow suppression. None of our patients suffered Hb drop which required blood transfusion pre, during or after

Table 1 Clinical data of SCA patients with chronic hepatitis

Total No. of patients	52
Sex	30 F: 22 M
Mean age (range)	29.5 (15-54) years
Mean HbS (range)	74.4% (66%-89%)
Mean HbF (range)	22.5% (9.6%-33.6%)
G6PD deficiency	12 (23.1%)
Mean HCV-RNA viral load (range)	986330 IU/mL (range 12762-3329282 IU/mL)
HCV genotype	
genotype 1	13 (8 non-responders)
genotype 2	20 (2 non-responders)
genotype 3	6
genotype 4	8 (4 non-responders)
genotype 5	1 (1 non-responder)
not available	4
Mean Hb level	
At start of treatment	10.2 g/dL (7.5-11.5 g/dL)
At 3 mo of treatment	10.4 g/dL (8.9-11.2 g/dL)
At 6 mo of treatment	10.35 g/dL (8.5-11.9 g/dL)
At the end of treatment	10.3 g/dL (8.2-11.7 g/dL)
SVR at 6 mo after the end of treatment	37 (71.2%)

SCA: Sickle cell anemia; SVR: Sustained viral response; HCV: Chronic hepatitis C.

therapy. Their mean hemoglobin level at the start of treatment was 10.2 g/dL (7.5-11.5 g/dL). There was no significant change in hemoglobin, LDH and bilirubin levels during or at the end of treatment. Their mean Hb level at 3 mo was 10.4 g/dL (8.9-11.2 g/dL), at 6 mo was 10.35 g/dL (8.5-11.9 g/dL) and at the end of treatment was 10.3 g/dL (8.2-11.7 g/dL). The lowest Hb level at the beginning of treatment was 7.5 g/dL. This patient did not receive pre-treatment blood transfusion and his Hb improved during treatment and at the end of treatment. His mean Hb during treatment was 9.6 g/dL (7.5-11.2 g/dL). The main adverse effects encountered in some of our patients were flu-like symptoms, headache, and loss of appetite and generalized body ache. These adverse effects were transient and tolerated by all patients. There were no more episodes of acute vaso-occlusive crisis, acute chest syndrome or other complications of sickle cell anemia while undergoing therapy. Thirty-seven (71.2%) of our patients achieved SVR at 6 mo after the end of treatment. The remaining 15 were non-responders. Two of them with an HCV genotype 2 showed an end of treatment response but had a relapse. The remaining 13 non responders had relatively significant HCV viral load with a mean HCV-RNA viral load 1829741.2 IU/mL (900000-3329282 IU/mL). Eight of them had HCV genotype 1, four had HCV genotype 4, and one had HCV genotype 5.

DISCUSSION

Patients with SCA frequently need blood transfusions to treat the various complications including acute and chronic anemia, splenic and hepatic sequestration crisis, acute chest syndrome, and priapism and central nervous system crisis. The need for blood transfusion in these patients starts early especially in those with hemolytic crisis, splenic sequestration crisis and acute chest syndrome. This puts them at potential risk for alloimmunization, iron overload and chronic viral hepatitis B and C[7,8]. Hepatitis C is one of the most common blood-born infections worldwide. This is more so in those who receive frequent blood transfusions, especially patients with thalassemia and SCA[10]. It is also well known that patients with HCV if left untreated are susceptible to liver damage, liver cirrhosis, hepatocellular carcinoma and liver failure. The combination of iron overload and HCV can lead to more rapidly progressive liver disease. The life expectancy of patients with SCA is known to have been shorter than the general population and they usually die of SCA-related complications. This however is not the case nowadays and as a result of better understanding of SCA and its complications, the use of hydroxyurea as well as improved care, SCA patients are living longer[11-13]. In the past there was no well proven treatment for HCV, but recent progress has made the treatment and cure of HCV possible[14-16]. The standard treatment for HCV is a combined therapy using pegylated interferon and ribavirin. Treatment response depends on several factors including HCV genotype[14-16]. A sustained virological response in up to 60% of HCV patients with genotype 1 and 4 and up to 90% in those with genotype 2 and 3 has been reported[15]. For many years, patients with SCA and HCV were considered to be unsuitable for such treatment. One reason for this is that ribavirin may induce hemolysis and severe anemia which can further aggravate patients' already existing anemia. Swaim *et al*[17] were the first to report successful treatment of two patients with SCA and HCV using interferon alpha-2b and ribavirin. Ancel *et al*[18] treated ten patients with HCV, five with thalassemia and five with SCA. Eight received pegylated interferon plus ribavirin while the other two were treated with pegylated interferon as a monotherapy. Nine out of 10 (90%) achieved a virological response and 6 (60%) went on to achieve sustained virological response after treatment was completed. Ayyub *et al*[20] reported eight patients with SCA and HCV who were treated with pegylated interferon alpha-2a and ribavirin for one year. All eight patients had a complete early virological response and five of them maintained a sustained virological response when assessed 6 mo after the end of treatment. Our series is the largest to be reported so far. We treated 52 SCA patients with HCV and 37 (71.2%) of them showed SVR 6 months after the end of treatment. This is comparable to the results reported by others and to those for non SCA patients treated for HCV[15,16,18-20]. It is also important to note that the dose of ribavirin was not reduced in any of our patients and the non-responders had a relatively high viral load which negatively predicts the response to treatment[22]. Eight of them also had HCV genotype 1; four had HCV genotype 4, 2 had HCV genotype 2 and one had HCV genotype 5.

In all the few reports of patients with thalassemia and HCV who were treated with interferon and ribavirin, there was an increase in their transfusion requirements[18,23-26]. Hamidah *et al*[24] reported a significant increase in the transfusion requirements of one patient with thalassemia and HCV who was treated with pegylated interferon alpha-2b and ribavirin. Telfer *et al*[25] treated 11 thalassemic patients with interferon and ribavirin and reported sustained virological response in 5 of them. There was however an increase in their transfusion requirements. Ancel *et al*[18] reported a 22% increase in the transfusion requirements of five patients with thalassemia and HCV treated with pegylated interferon and ribavirin. Li *et al*[26] reported a 30% increase in the transfusion requirement of a group of patients with thalassemia treated for HCV with interferon alpha-2b and ribavirin. In general, this was due to ribavirin-induced hemolysis. This however was not the case for patients with SCA where it was shown that either there was no change in their Hb level or in some of them there was actually an increase in their Hb level[17-20]. This was also shown in our series where none of our patients required blood transfusion during or at the end of treatment and in none of them there was a need to decrease the dose of ribavirin or discontinue treatment. The reason for this difference between patients with thalassemia and SCA in this regard is not known. One contributing factor is hydroxyurea which is currently used to ameliorate the severity of SCA by increasing patients HbF levels[11,12]. It was postulated that an increase in the HbF level in these patients may decrease the chance of ribavirin-induced hemolytic anemia. Because of this it was recommended to start and maintain these patients on hydroxyurea prior to therapy with ribavirin. SCA patients from the Eastern Province of Saudi Arabia are known to have high levels of HbF which is a contributing factor for the mildness of SCA in our patients[27]. Our patients had a high mean HbF level of 22.5% (9.6%-33.6%). Only 8 of them were on hydroxyurea and their mean HbF level was 19.8% (11.5%-28.2%). These were started on hydroxyurea treatment prior to the decision to treat them for HCV and none of the remaining patients were intentionally started on hydroxyurea. There was no difference between those who were on hydroxyurea and those who did not receive hydroxyurea in terms of response to treatment or complications. We feel that the use of hydroxyurea prior to or during therapy for HCV in patients with SCA, although beneficial is not a necessity or a prerequisite for the treatment of HCV. This is especially so in our setting where our patients are already having high levels of HbF It is also well known that ribavirin causes a dose-dependent hemolytic anemia. Another measure to decrease or avoid ribavirin-induced hemolysis was to start these patients at a lower dose of ribavirin as suggested by Ancel *et al*[18]. Their patients received pegylated interferon at full dose while ribavirin was started at the lower dose of 200 mg twice daily and increased gradually until the full recommended dose was reached, usually within 4-8 wk from the beginning of therapy. This was also the case for all the patients reported by Ayyub *et al*[20]. Their patients were treated with pegylated interferon alpha-2a, 180 micrograms subcutaneously once per week and an initial dose of ribavirin 200 mg twice daily, increased gradually to 400 mg twice daily over a period of 4-8 wk. All our patients with HCV genotype 2 and 3 and those in whom the genotype was not available were started on 400 mg ribavirin twice daily and those with HCV genotype 1, 4 and 5 received 600 mg of ribavirin twice daily. None of our patients developed hemolysis, anemia or bone marrow suppression. We feel that patients with SCA and HCV can tolerate from the start the full dose of 400 mg of ribavirin twice daily for those with HCV genotypes 2 and 3 and up to 600 mg twice daily for those with genotypes 1 and 4 without subjecting them to additional major side effects.

In conclusion, patients with SCA and HCV can be treated with pegylated interferon and the usual recommended dose of ribavirin. This is even so for those who are not receiving hydroxyurea. The treatment is safe and effective and the response rate is comparable to those without SCA. There were no hematological side effects attributable to ribavirin even at the usual recommended dose. These patients however need to be followed-up closely while on therapy by a hematologist and a gastroenterologist. Further studies are important in this regard to establish definite guidelines for the treatment of SCA patients with HCV.

COMMENTS

Background

Sickle cell anemia (SCA) is one of the common hemoglobinopathies in the world. It is well known that SCA can affect any part of the body and that patients are liable to transfusion related hepatitis B and C. The life expectancy of patients with SCA has improved considerably and this is attributed to better understanding of the disease, improved medical and surgical management and the use of hydroxyurea. Improved life expectancy will put SCA patients with chronic hepatitis B and C at risk of developing liver cirrhosis, hepatocellular carcinoma and liver failure if their hepatitis B and C are not treated. In spite of the markedly improved results in the treatment of chronic hepatitis C using the combined therapy of pegylated interferon and ribavirin, patients with SCA and chronic hepatitis C were not previously considered suitable for such treatment because of the believed risk that ribavirin would induce hemolysis and severe anemia which could aggravate their already existing anemia.

Research frontiers

There have been three publications reporting success of such treatment in patients with SCA and HCV C although the number of patients reported was small and dose of ribavirin was not the standard.

Innovations and breakthroughs

The standard treatment for HCV is a combined therapy using pegylated interferon and ribavirin. Treatment response depends on several factors including HCV genotype. Patients with SCA and HCV were, for many years, considered to be unsuitable for such treatment. One reason for this is that ribavirin may induce hemolysis and severe anemia which can further aggravate already existing anemia. It is also well known that ribavirin causes a dose-dependent hemolytic anemia. In the previous studies patients were started at a lower dose of ribavirin as a measure to decrease or avoid ribavirin-induced hemolytic anemia. These patients received pegylated interferon at full dose while ribavirin was started at a lower dose of 200 mg twice daily and increased gradually until the full recommended dose was reached, usually within 4-8 wk from the beginning of therapy. This may have an impact on the RVR or SVR. All our patients with HCV genotype 2 and 3 and those in whom the genotype was not available were started on 400 mg ribavirin twice daily while those with HCV genotype 1, 4 and 5 received 600 mg of ribavirin twice daily. None of our

patients developed hemolysis, anemia or bone marrow suppression. Our series is the largest to be reported so far. We treated 52 SCA patients with HCV and 37 (71.2%) of them showed SVR. It was also postulated that an increase in the HbF level in these patients may decrease the chance of ribavirin induced hemolytic anemia. Because of this it was recommended to start and maintain these patients on hydroxyurea prior to therapy with ribavirin. Our patients had a high mean HbF level of 22.5% (9.6%-33.6%). We feel that the use of hydroxyurea prior to or during therapy for HCV in patients with SCA, although beneficial, is not a necessity or a prerequisite for the treatment of HCV. This is especially so in our setting where our patients already have high levels of HbF.

Applications

Patients with SCA and HCV can be treated safely with pegylated interferon in the usual recommended dose of ribavirin without subjecting them to additional major side effects. We feel that patients with SCA and HCV can tolerate from the start the full dose of 400 mg of ribavirin twice daily for those with HCV genotypes 2 and 3 and up to 600 mg twice daily for those with genotypes 1 and 4. This is even so for those who are not receiving hydroxyurea. The treatment is safe and effective and the response rate is comparable to those without SCA.

Peer review

The author presents a nice-sized case series of sickle-cell anemia patients treated for hepatitis C successfully. The paper adds to the literature and provides evidence that this population can be safely given ribavirin.

REFERENCES

1 **Perrine RP**, Pembrey ME, John P, Perrine S, Shoup F. Natural history of sickle cell anemia in Saudi Arabs. A study of 270 subjects. *Ann Intern Med* 1978; **88**: 1-6
2 **Al-Awamy BH**. Sickle cell anemia, its clinical manifestations and their management. *Saudi Med J* 1987; 9: 553-562
3 **Krauss JS**, Freant LJ, Lee JR. Gastrointestinal pathology in sickle cell disease. *Ann Clin Lab Sci* 1998; **28**: 19-23
4 **Shao SH**, Orringer EP. Sickle cell intrahepatic cholestasis: approach to a difficult problem. *Am J Gastroenterol* 1995; **90**: 2048-2050
5 **Bauer TW**, Moore GW, Hutchins GM. The liver in sickle cell disease. A clinicopathologic study of 70 patients. *Am J Med* 1980; **69**: 833-837
6 **Schubert TT**. Hepatobiliary system in sickle cell disease. *Gastroenterology* 1986; **90**: 2013-2021
7 **Hassan M**, Hasan S, Giday S, Alamgir L, Banks A, Frederick W, Smoot D, Castro O. Hepatitis C virus in sickle cell disease. *J Natl Med Assoc* 2003; **95**: 939-942
8 **DeVault KR**, Friedman LS, Westerberg S, Martin P, Hosein B, Ballas SK. Hepatitis C in sickle cell anemia. *J Clin Gastroenterol* 1994; **18**: 206-209
9 **Memish ZA**, Knawy BA, El-Saed A. Incidence trends of viral hepatitis A, B, and C seropositivity over eight years of surveillance in Saudi Arabia. *Int J Infect Dis* 2010; **14**: e115-e120
10 **Al-Faleh FZ**, Sami Ramia, S. Hepatitis C virus (HCV) infection in Saudi Arabia: A review. *Ann Saudi Med* 1997; **17**: 77-82
11 **Steinberg MH**. Hydroxyurea treatment for sickle cell disease. *Scientific World Journal* 2002; **2**: 1706-1728
12 **Steinberg MH**, Barton F, Castro O, Pegelow CH, Ballas SK, Kutlar A, Orringer E, Bellevue R, Olivieri N, Eckman J, Varma M, Ramirez G, Adler B, Smith W, Carlos T, Ataga K, DeCastro L, Bigelow C, Saunthararajah Y, Telfer M, Vichinsky E, Claster S, Shurin S, Bridges K, Waclawiw M, Bonds D, Terrin M. Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia: risks and benefits up to 9 years of treatment. *JAMA* 2003; **289**: 1645-1651
13 **Vichinsky EP**. Comprehensive care in sickle cell disease: its impact on morbidity and mortality. *Semin Hematol* 1991; **28**: 220-226
14 **Lauer GM**, Walker BD. Hepatitis C virus infection. *N Engl J Med* 2001; **345**: 41-52
15 **Manns MP**, McHutchinson JG, Gordon S. Peginterferon alfa-2b plus ribavirin compared to interferon alfa-2b plus ribavirin for the treatment of chronic hepatitis C: 24 week treatment analysis of a multicenter, multinational phase III randomized controlled trial. *Hepatology* 2000; **32**: A297-A297
16 **Fried MW**, Shiffman ML, Reddy KR, Smith C, Marinos G, Gonçales FL Jr, Häussinger D, Diago M, Carosi G, Dhumeaux D, Craxi A, Lin A, Hoffman J, Yu J. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002; **347**: 975-982
17 **Swaim MW**, Agarwal S, Rosse WF. Successful treatment of hepatitis C in sickle-cell disease. *Ann Intern Med* 2000; **133**: 750-751
18 **Ancel DB**, Chaslin-Ferbus D, Amiot, XJ. Treatment of chronic hepatitis C in thalassemic and sickle cell disease patients with interferon alfa2b (IFN) and ribavirin (RBV). Los Angeles, CA. *DDW* 2006: A198
19 **Ancel D**, Amiot X, Chaslin-Ferbus D, Hagege I, Garioud A, Girot R, Pol S, Grange JD. Treatment of chronic hepatitis C in sickle cell disease and thalassaemic patients with interferon and ribavirin. *Eur J Gastroenterol Hepatol* 2009; **21**: 726-729
20 **Ayyub MA**, El-Moursy SA, Khazindar AM, Abbas FA. Successful treatment of chronic hepatitis C virus infection with peginterferon alpha-2a and ribavirin in patients with sickle cell disease. *Saudi Med J* 2009; **30**: 712-716
21 **Poynard T**, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. *Lancet* 1997; **349**: 825-832
22 **Vichinsky EP**. Current issues with blood transfusions in sickle cell disease. *Semin Hematol* 2001; **38**: 14-22
23 **Nunez M**, Marino A, Miralles C, Berdun MA, Sola J, Hernandez-Burruezo JJ. Baseline serum hepatitis C virus (HCV) RNA level and response at week 4 are the best predictor of relapse after treatment with pegylated interferon plus ribavirin in HIV/HCV-coinfected patients. *JAIDS* 2007; **45**: 439-444
24 **Hamidah A**, Thambidorai CR, Jamal R. Peginterferon alfa-2b and ribavirin in thalassaemia/chronic hepatitis C virus-co-infected non-responder to standard interferon-based. *Med J Malaysia* 2005; **60**: 517-519
25 **Telfer PT**, Garson JA, Whitby K, Grant PR, Yardumian A, Hoffbrand AV, Wonke B. Combination therapy with interferon alpha and ribavirin for chronic hepatitis C virus infection in thalassaemic patients. *Br J Haematol* 1997; **98**: 850-855
26 **Li CK**, Chan PK, Ling SC, Ha SY. Interferon and ribavirin as frontline treatment for chronic hepatitis C infection in thalassemia major. *Br J Hematol* 2002; **117**: 755-758
27 **Al-Awamy BH**, Niazi GA, el-Mouzan MI, Altorki MT, Naeem MA. Relationship of haemoglobin F and alpha thalassaemia to severity of sickle-cell anaemia in the Eastern Province of Saudi Arabia. *Ann Trop Paediatr* 1986; **6**: 261-265

S- Editor Zhang HN **L- Editor** Hughes D **E- Editor** Liu N