Combination therapy with interferon and ribavirin for chronic hepatitis C infection in beta-thalassaemia major

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المعالجة المشتـركة لالتهاب الكبد المزمن سي لدى المصابين بالتلاسيميا بيتا الكبرى بالإنتـرفيرون والريبافيـرين

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الخلاصـة: تتعقَّد معالجة العدوى بالتهاب الكبد المزمن سي لدى المصابين بالتلاسيميا بيتا الكبرى المعتمدين على نقل الدم بتـراكم الحديد في الكبد وبالخوف من انحلال الدم المرافق للمعالجة بالريبافيرين. وقد قيَّم الباحثون كفاءة المعالجة المشتـركة بالانتـرفيون ألفا والريبافيرين لدى مرض التلاسيميا المصابين بعدوى الفيروس سي لالتهاب الكبد وما يرافق تلك المعالجة من تأثيرات جانبية. وقد شملت الدراسة 17 مريضاً (كان 10 منهم من غير المستجيبين للمعالجة بالإنتـرفيرون لوحده، و7 منهم يعالجون لأول مرة، وكان وسطي العمر لديهم 23.1 عاماً). وقد تلقوا جميعهم المعالجة المشتـركة لمدة 12 شهراً، فبلغ معدَّل الاستجابة الفيرلوجية المستقرّة بعد 6 شهور من المعالجة 58.8٪. وقد ازدادت متطلبات نقل الدم المؤقتة أثناء المعالجة بمقدار 36.6٪. وقد تحمل مرضى التلاسيميا الكبرى المصابين بعدوى فيروس التهاب الكبد سي المعالجة المشتـركة تحملاً جيداً، وقد تكون مفيدة لهم.

ABSTRACT Treatment of chronic hepatitis C virus (HCV) infection in transfusion-dependent beta-thalassaemia major patients is complicated by existing hepatic siderosis and the fear of ribavirin-associated haemolysis. We evaluated the efficacy and side-effects of combination interferon-α (INF) and ribavirin therapy for HCV-infected thalassaemia patients. A total of 17 patients were enrolled (10 nonresponders to INF monotherapy, 7 naive to treatment, mean age 23.1 years) and they received 12 months of combination therapy. The sustained virological response rate 6 months after treatment was 58.8%. Blood transfusion requirements during treatment temporarily increased by 36.6%. Combination therapy was tolerated by, and may be useful for, HCV-infected thalassaemia major patients.

Thérapie combinée par interféron et ribavirine pour soigner l'infection chronique par le virus de l'hépatite C dans les cas de bêta-thalassémie majeure

RÉSUMÉ Le traitement de l'infection chronique par le virus de l'hépatite C (VHC) chez les patients atteints de bêta-thalassémie majeure et dépendants des transfusions est compliqué par l'existence d'une sidérose hépatique et par la crainte de l'hémolyse associée à la ribavirine. Nous avons évalué l'efficacité et les effets secondaires de la thérapie combinée par interféron α et ribavirine chez des thalassémiques infectés par le VHC. Au total, 17 patients ont été recrutés pour l'étude (10 ne répondaient pas à la monothérapie par interféron, 7 n'avaient pas encore reçu de traitement, moyenne d'âge 23,1 ans) et ont reçu la thérapie combinée pendant 12 mois. Le taux de réponse virologique prolongé six mois après le traitement était de 58,8 %. La nécessité de transfusions sanguines pendant le traitement a provisoirement augmenté de 36,6 %. La thérapie combinée était tolérée par les malades atteints de thalassémie majeure infectés par le VHC et peut leur être bénéfique.

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Introduction

Hepatitis C virus (HCV) infection is common in patients receiving long-term blood transfusion therapy [*1–5*]. In the case of patients with beta-thalassaemia major (TM), hepatic damage due to HCV infection is exacerbated by iron overload due to transfusion, and liver disease is a recognized cause of mortality [*6*]. The therapeutic aim in HCV infection, especially in TM patients, is the early eradication of the virus in order to avoid long-term clinical complications [*7*]. Current evidence indicates that combination therapy with interferon [interferon-2α (INF) or pegylated interferon-α] and ribavirin (Rib) for HCV infection is associated with higher rates of sustained virological, biochemical and histological responses compared with INF alone [*8–10*]. However, reversible haemolytic anaemia, the major toxicity associated with Rib therapy, is a limiting factor for the use of Rib in patients with underlying haemolytic anaemia, and can cause further problems with anaemia because these patients are prone to constant haemolysis [*11–14*].

This report reviews the response to INF and Rib combination therapy in chronic HCV-infected TM patients who did not respond or relapsed to INF monotherapy and/or were naive to HCV treatment in Sari, Islamic Republic of Iran.

Methods

Patients

Between April 2000 and April 2005, 17 transfusion-dependent TM patients were consecutively enrolled into a noncontrolled, descriptive study of 12 months of INF and Rib combination therapy at the thalassaemia hepatitis centre at Boali-Sina hospital, Sari, Islamic Republic of Iran. These HCV-infected TM patients were selected from a previous study [*15*]. In that study 77 (15%) patients were found to have seroprotective titres in an HCV-infection screening of 500 TM patients at Sari thalassaemia centre. After approval of the ethics committee and with informed written consent from patients and parents, liver biopsy was performed on 42 patients; 33 were treated with INF for 9–12 months. Virological response occurred in 60% of treated patients. Untreated patients, i.e. those who were unresponsive to INF therapy or relapsed, were included in the study reported here.

The inclusion criteria were: chronic HCV-infected TM patients who failed to respond or relapsed to INF monotherapy or were naive to treatment, and seropositivity for anti-HCV antibodies. HCV status was determined using 3rd generation enzyme-linked immunosorbent assay (ETI-AB-HCV K-3, DiaSorin, Vercelli, Italy) and reconfirmed by HCV-RNA, using a qualitative polymerase chain reaction (PCR) assay (genotyping was not possible), the presence of abnormal serum alanine aminotransferase (ALT) levels (≥ 1.5-fold normal values) for 6 months and a diagnosis of chronic hepatitis determined from liver biopsy performed within the preceding 6–12 months.

The exclusion criteria included: decompensated liver disease; symptomatic cardiac or renal impairment; psychiatric or autoimmune diseases; leukopenia ($< 2 \times 10^9$ cells/L) or thrombocytopenia ($< 100 \times 10^9$ cells/L); and serological evidence of hepatitis B virus and or human immunodeficiency virus infection. All patients and their parents were informed about the purpose of the study and the known side-effects with both drugs, and were asked to sign a consent form.

Treatment regimen and monitoring

Recombinant INF (pegferon-B3 MioIU, Pooyesh-Darou, Tehran, Islamic Republic

of Iran), 3 MU 3 times weekly subcutaneously, was administered together with Rib (Ribacip-200, Cipla, Mumbai, India), 800 mg daily orally in 2 divided doses, up to 4 months after virological response or a maximum of 9 months if there was no response. The treatment duration was 12 months, during which the pretransfusion haemoglobin level was maintained at 9–11 g/dL with more frequent transfusion if required, and iron chelation therapy with desferrioxamine was increased with increased blood consumption.

Baseline assessment was the number of units of red blood cells transfused during the 12 months prior to therapy. Patients were seen at weeks 1, 2, 4 and 6 and every 3–4 weeks thereafter for assessment of compliance, adverse effects, blood transfusion requirements and full blood count. Dosage adjustment was allowed for INF if the patients developed leukopenia (< 2000 cells/mL) or thrombocytopenia (< 100 000 cells/mL). The dosage of Rib was not adjusted as these patients were all transfusion-dependent.

Biochemical monitoring included ALT testing on alternate months and serum ferritin testing at 3-month intervals. The virological response was assessed by serum HCV-RNA detection at months 4, 8 and 12 during treatment and for at least 6 months after completion of treatment. Sustained virological and biochemical responses were defined as disappearance of HCV-RNA and normalization of ALT for 6 months after completion of treatment.

Analysis

Paired *t*-tests were used to compare ALT levels, serum ferritin concentration and mean blood consumption before and after treatment. $P < 0.05$ was considered significant.

Results

A total of 17 HCV-infected TM patients (11 males) consented to treatment; 7 patients were naive to treatment and 10 had been treated before (5 non-responders, 5 relapsers). The mean age of patients was 23.1 (range 17–34) years, and the mean duration of blood transfusion was 19.9 (range 13.5–29) years. The mean serum ferritin and ALT levels before treatment were 1782 µg/L [standard deviation (SD) 659], and 125 IU/L (SD 51) respectively. Three (3) patients required transient reduction of INF dose for 2 weeks because of mild leukopenia. All patients completed the 9–12 months treatment.

Serum HCV-RNA became undetectable in 8 patients after 4 months and in a further 4 patients by 12 months. However, 2 initial responders showed reappearance of HCV-RNA 6 months after treatment. The sustained virological response rate was 10/17 patients (58.8%). Comparing serum HCV-RNA clearing rates according to the pretreatment status of the patients indicated that 5/10 (50.0%) previously treated, and 5/7 (71.4%) naive patients showed sustained virological clearance. Biochemical response occurred earlier than virological response, and was achieved in 13 (76.5%) cases. Serum ferritin levels remained stable during treatment in both responders and nonresponders respectively [1435 (SD 1241) µg/L versus 1946 (SD 1073) µg/L)] ($t = 0.75$, $P = 0.45$).

Side-effects of fever, chill, malaise and headache were common but transient. There was no weight reduction. The most significant complication was Rib-associated haemolysis. The patients required more frequent transfusion to maintain a pretransfusion haemoglobin level of about 9–11 g/dL compared with the transfusion require-

ments during the 12-month period prior to treatment [mean 4353 mL/year/patient pretreatment (SD 1241) versus 5947 (SD 1278) mL/year/patient during the treatment period]. During treatment the mean blood consumption per patient rose from 4353 to 5947 mL/year, a 36.6% increase (range 3.0% to 112%). After treatment, blood consumption reduced to pretreatment levels.

All the results are shown in Table 1.

Discussion

The results of this study showed that with INF and Rib combination therapy, sustained clearance of serum HCV-RNA can be obtained in more than half of TM patients with chronic HCV infection who have failed INF monotherapy or were naive to HCV treatment. The major side-effect was a significant increase in the need for transfusion during the treatment.

A combination of INF (or pegylated interferon-α) and Rib therapy has been shown to be superior to INF monotherapy as treatment of choice in non-TM patients [*8–10*]. The benefits of this form of therapy may significantly outweigh the risks associated with the increased haemolysis even in TM patients. However, data on combination therapy in TM patients are limited and most reports are based on INF monotherapy [*16,17*].

Limited case series have shown that the addition of Rib to INF improves the virological response rate to 45%–72%, albeit at the cost of a 30%–50% increase in blood transfusion requirements during the treatment period [*18,19*]. In a study by Telfer et al., INF in combination with Rib produced sustained virological response rates of 45% in 11 HCV-infected transfusion-dependent TM patients in whom INF monotherapy failed [*18*]. The use of combination therapy in 18 previously untreated HCV-infected TM patients by Li et al. revealed that 72.2% of treated patients showed sustained virological clearance [*19*]. Another study on the efficacy and tolerability of pegylated interferon-α with or without Rib in chronic HCV-infected TM patients showed that 62.5%and 30.0% of patients got a sustained virological response to combination and monotherapy respectively [*20*].

The overall serum HCV-RNA viral clearance rate achieved in our study was 58.8%, more than the 45% rate achieved by Telfer et al. [*18*], but lower than the 72.2% obtained by Li et al. [*19*]. Although the number of patients in our study was too small to be divided into 2 subgroups, when the comparison of serum HCV-RNA clearing rates were made according to the pretreatment status of the patients, the results indicated that 5 out of 10 (50.0%) of previously treated, and 5 out of 7 (71.4%) of naive patients showed sustained virological clearance. These values are in accordance with results of the above-mentioned studies [*18–20*].

The most important side-effect associated with combination therapy is a significant increase in haemolysis [*11–14*], leading to a greater need for transfusion. This may put these patients at risk of a further increase in iron overload during combination therapy. Therefore, patients should be instructed to intensify desferrioxamine chelation during treatment [*21*]. Our study demonstrated an average 36.6% increase in blood consumption during therapy, which is consistent with the studies of Telfer et al. [*17*], Li et al. [*18*] and Inati et al. [*19*] where the levels of blood consumption were increased by 41%, 30% and 34% respectively.

Serum ferritin levels remained static during the treatment period. However, in

Table 1 **Baseline characteristics of beta thalassaemia major patients and their response to ribavirin/interferon combination therapy**

Case[a]	Age (years)	Transfusion duration (years)	Chelation	Ferritin level (µg/L)		ALT level (IU/L)		HCV-RNA response[b]			Blood consumption (mL/year)	
				Pre Rx	Post Rx	Pre Rx	Post Rx	During Rx		Post Rx	Pre Rx	During Rx
								4 m	12 m	6 m		
1	25	21.0	DFO	1029	939	175	38	+	+	+	2850	4300
2	24	77.0	DFO	1871	976	75	68	+	–	+	2800	5200
3	18	13.0	DFO	2802	2300	140	34	+	–	–	3800	5600
4	25	21.0	DFO	1590	1210	61	26	–	–	+	4200	6100
5	23	21.5	DFO+L1	2380	1989	135	22	+	+	+	4500	6350
6	19	18.5	DFO	2522	2114	219	186	+	+	+	3500	5350
7	23	22.0	DFO	2242	960	213	23	+	–	–	3000	3100
8	34	29.0	DFO	1496	601	189	36	–	–	–	4200	8900
9	23	17.5	DFO	1028	1000	128	20	–	–	–	3100	5700
10	25	22.0	DFO	1753	1338	124	22	+	–	–	6500	7200
11	22	19.0	DFO	1149	1268	135	112	+	+	+	7000	7600
12	25	21.0	DFO+L1	3100	2580	84	32	–	–	–	3100	6100
13	23	19.0	DFO	2186	1496	60	84	+	+	+	4700	6200
14	23	21.0	DFO+L1	1038	2200	124	22	–	–	–	5050	5300
15	17	15.5	DFO	1690	801	68	21	–	–	–	5650	6600
16	23	19.5	DFO	1330	1300	112	32	–	–	–	5650	5900
17	21	19.5	DFO	1110	980	86	28	–	–	–	4400	5600

[a]Patient 1–10 were hepatitis C virus-infected beta thalassaemia major cases without response to interferon-2α monotherapy (1–5 nonresponders, 6–10 relapsers) and patients no. 11–17 were naive to treatment.

[b]At 4 months during treatment, at 12 months during treatment and 6 months after treatment.

Rx = treatment; DFO = desferrioxamine; L1 = deferiprone; ALT = alanine aminotransferase; HCV-RNA = hepatitis C virus ribonucleic acid test result.

responders there was not statistically significant ($P = 0.45$) decline in serum ferritin levels which might just reflect a decrease in hepatitis activity.

The main limitation of our study was the small number of patients enrolled, primarily as a result of the declining number of patients with TM and HCV; this fact is evident in the literature, where the largest cohort of patients receiving combination therapy consisted of 18 patients.

Conclusion

In conclusion, considering that the risks associated with increased transfusion requirements for a few months are outweighed by the benefits, this small study confirms that the combination of INF and Rib is effective, probably safe, and should be considered as the first-line therapy in cases of HCV-infected transfusion-dependent TM patients, who fail to respond to INF monotherapy.

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International consultative workshop on preventive measures against infectious disease for Hajj and Umra concluded in Saudi Arabia

The Government of Saudi Arabia held a 4-day international consultative workshop on infectious disease control and prevention for Hajj and Umra on 27–30 June, where concerns about the ongoing influenza A(H1N1) pandemic and the potential for transmission in crowded settings were discussed.

The panel for the consultation included local and regional experts and international experts from WHO, the Centers for Disease Control and Prevention (CDC), the European Centre for Disease Prevention and Control (ECDC) and other institutions in Europe, Australia and China. Based on consideration of the existing scientific evidence regarding mass gathering and the special settings of Hajj and Umra in particular, and the implications for local and global health, recommendations were made to the Government of Saudi Arabia.

Futher information can be found in the WHO EMRO Press release, 1 July, 2009 (http://www.emro.who.int/pressreleases/2009/no15.htm).