Treatment of hepatitis C virus genotype 4 with peginterferon alfa-2a: Impact of bilharziasis and fibrosis stage

MF Derbala, SR Al Kaabi, NZ El Dweik, F Pasic, MT Butt, R Yakoob, A Al-Marri, AM Amer, N Morad, A Bener

AIM: To evaluate pegylated interferon alpha2a (PegIFN-α2a) in Egyptian patients with HCV genotype 4, and the impact of pretreatment viral load, co-existent bilharziasis and histological liver changes on response rate.

METHODS: A total of 73 naïve patients (61 with history of bilharziasis) with compensated chronic HCV genotype 4 were enrolled into: group A (38 patients) who received 180 mg PegIFN-alpha2a subcutaneously once weekly for a year and group B (35 patients) received IFN alpha-2a 3 MU 3 times weekly. Ribavirin was added to each regimen at a dose of 1200 mg. Patients were followed for 72 wk and sustained response was assessed.

RESULTS: Significant improvement in both end of treatment response (ETR) ($P < 0.002$) and sustained response (SR) ($P < 0.05$) was noted with pegylated interferon, where ETR was achieved in 29 (76.3%) and 14 patients (40%) in both groups respectively, and 25 patients in group A (65.8%) and 9 (25.7%) in group B could retain negative viraemia by the end of follow up period. Sustained virological response (SVR) showed a significant negative correlation with age and positive correlation with pretreatment inflammation in patients receiving PegIFN. Viral clearance after 3 mo of therapy was associated with high incidence of ETR and SR ($P < 0.001$), but without significant difference between both forms of interferon. Significant improvement in response was achieved in patients with high grade fibrosis (grade 3 and 4) with PegIFN-α2a, where SR was seen in 5 out of 13 patients in group A, but none in group B. There was no significant difference in response between bilharzial and non-bilharzial patients in both groups. In terms of safety and tolerability, neutropenia was the predominant side effect; both drugs were comparable.

CONCLUSION: PegIFN-α2a combined with ribavirin results in improvement in sustained response in HCV genotype 4, irrespective of history of bilharzial infestation.

© 2006 The WJG Press. All rights reserved.

Key words: Hepatitis C virus; Genotype 4; Pegsys; Bilharziasis

INTRODUCTION

Hepatitis C is comparable to a ‘viral time bomb’. The WHO estimates that about 200 million people, 3% of the world’s population, are infected with hepatitis C virus (HCV) and 3 to 4 million persons are newly infected each year. The striking genetic heterogeneity of RNA genome of HCV is well recognized. Six major genotypes and over 50 subtypes and minor variants referred to as "quasispecies" are described[8]. HCV genotype differences seem to be of considerable clinical significance because they affect the responses to antiviral therapy[9]. HCV genotype 4 appears to be prevalent in the Middle East and Central Africa, where almost 13% of HCV carriers around the world live in the Eastern Mediterranean region. Prevalence rates of HCV genotype 4 ranges from 60% in Saudi Arabia to 90% in Egypt where it has been reported to be frequently associated with cirrhosis and a poor response to interferon (IFN)[10].

Concurrent HCV-genotype 4 infection and schistosomiasis result in a much more severe liver disease than that seen with either disease alone. Luckily, the activity of HCV infection seems to be partially suppressed in such patients[8]. The effect of such co-infection on hepatic fibrosis and in turn on response to treatment in HCV patients is however, conflicting. While Helal et al in 1989[10] and Shiha et al in 2002[7] reported a lack of enhancement.
of hepatic pathology in the schistosomal patients, Hassan et al in 2002\[8\] suggested that schistosomiasis is an important risk factor involved in enhancement of nitric oxide levels and virus replication, which in turn may aggravate liver cell injury and hence the development of cirrhosis.

It has been reported that treatment with conventional IFN is less effective in patients with genotypes 1 and 4 than in patients with genotypes 2 and 3\[9\]. The high rate of HCV turnover coupled with the short half-life of the drug, limits the efficacy of conventional IFN therapy\[10\]. Pegylated IFN-α2a [Peg-IFN-α2a (40 kDa); Pegasys, Hoffmann-La Roche] is produced by attachment of a 40 kDa branched polyethylene glycol moiety to IFN-α2a by a stable amide bond. It is characterized by prolonged absorption half-life, restricted volume distribution, and decreased clearance compared to standard interferon, which thus increase its therapeutic efficacy with less frequent doses\[10\]. Recent clinical trials have shown that the response to pegylated interferon α2a plus ribavirin (RBV) therapy for chronic HCV infection is superior to that achieved with standard interferon α2a plus ribavirin therapy or peginterferon-α2a alone with a rapid decline in viral load in the first 12 wk, for all HCV genotypes\[12\]. Hematological adverse effects in the form of anemia, neutropenia and thrombocytopenia are the primary laboratory abnormalities experienced during IFN plus RBV combination therapy and may necessitate dose modification and thus potentially impact outcome. This anemia is attributed to both ribavirin dose-dependent hemolysis and direct suppressive effect of interferon on erythropoiesis\[10\]. Hematopoietic growth factors may be useful in the management of these side effects.

The purpose of this prospective analysis is to compare the effectiveness and safety of Pegasis (40 kDa) IFN-α2a once weekly with IFN-α2a, in compensated HCV genotype 4, in combination with ribavirin. The effect of pretreatment viral load, histological liver changes and schistosomiasis co-infection on response to treatment is also assessed.

**MATERIALS AND METHODS**

**Patients**

Adult patients with chronic active hepatitis C as evidenced by positive serological test for HCV-Ab using enzyme linked immunosorbent assay (ELISA) (Ortho Diagnostics, Neckargmün, Germany), detectable serum HCV-RNA by RT-PCR (Amplicor Molecular System, Hoffmann-La Roche, Basel, Switzerland), elevated serum alanine transaminases (ALT) activity more than twice the normal value and histopathological criteria of chronic active hepatitis. Liver histology was classified according to Scheuer score system from 0-4 for both grades (necroinflammation) and stage (degree of fibrosis). Hepatocellular carcinoma was excluded by testing of α-fetoprotein and by ultrasound scanning. None of the female patients was pregnant as evidenced by negative serum pregnancy test. Breast feeders were excluded. All patients had normal serum direct and indirect bilirubin, albumin and creatinine. All patients were genotype 4 detected by the Inno LiPA HCV II assay (Innogenetics Inc., GA, USA). Patients were excluded if co-infected with HBV, HIV. Hemochromatosis, Wilson disease or other causes for chronic liver disease were also ruled out. Other exclusion criteria included neutrophil count < 1.5 × 10^9/L, platelet count < 90 × 10^9/L or haemoglobin (Hb) < 100 g/L for female and < 110 g/L for male, positive auto-antibodies including antinuclear antibody (ANA), antimitochondrial antibody (AMA), anti-smooth muscle autoantibody (ASMA), patients with a history of severe psychiatric disease, seizure disorder, organ transplantation, or severe cardiac or pulmonary disease. All patients had normal thyroid function prior to the study and all were either non-diabetics or with controlled blood glucose level with hemoglobin A1C < 8.5%. Patients were excluded if they had clinically significant retinal abnormalities, clinical gout, were a substance abuser (alcohol or I.V. drugs) or showed any medical condition requiring systemic steroids.

**Safety assessment**

Patients were reviewed in the Hepatology Outpatient Clinic weekly during the first month and monthly thereafter along the course of therapy to check for safety, and then followed for at least 6 mo after discontinuation of treatment to assess for sustained response. Epoetin beta (Recormon®. Roche) at a dose of 4000 U/weekly for 2 wk was given when Hb level decrease > 30 mg/L or > 25% from baseline levels. Also Filgrastim (Neupogen®. Amgen. Inc. F. Hoffmann-La Roche Ltd. Basel) 5 μg/kg was given once or twice weekly if neutrophils < 0.7 × 10^9/L, while drug was discontinued completely for any patient showing Hb level < 85 g/L, neutrophils < 0.5 × 10^9/L, platelet < 50 × 10^9/L, abnormal thyroid function tests, creatinine > 177 μmol/L, or ALT/AST double baseline levels. Patients requiring modification of more than 4 doses were excluded.

**Efficacy assessment**

The primary efficacy end point was sustained response (SR), defined as undetectable HCV RNA and normal ALT level at the end of follow up (24 wk after discontinuation of treatment). The relapse rate was calculated as percentage of patients with an end-of-treatment response in whom HCV RNA was detectable at wk 72. End of treatment response (ETR) was defined as normalization of ALT and loss of detectable serum HCV RNA at the end of treatment.

**Study design**

This randomized, controlled clinical trial was conducted from February 2002 to November 2004. The study consisted of a screening phase, which began 2 mo prior to the first dose of the drug under evaluation. Examination established eligibility of patients according to inclusion/exclusion criteria. After a written informed consent was obtained in accordance with the Helsinki Declaration of 1979, 80 patients were randomly assigned at a 1:1 ratio to receive either, subcutaneously, once weekly 180 μg of peginterferon-α2a (Pegasys, Hoffmann-LaRoche) or IFN α2a (Roferon®, Hoffmann-LaRoche) 3 MU 3 times. Ribavirin 1200 mg at a daily oral dose was added to both.
regimens. Throughout the study, patients were monitored for vital signs, weight, adverse events, medication compliance, thyroid function, haematologic parameters, blood chemistry and serum HCV-RNA levels.

**Statistical analysis**

The data were coded, and processed on an IBM-PC compatible computer using Statistical Packages for Social Sciences (SPSS). Data were expressed as mean and standard deviation (SD) unless otherwise stated. Student’s t-test was used to ascertain the significance of difference between mean values of two continuous variables and Mann-Whitney test was used for non-parametric distribution. Chi-Square analysis was performed to test for differences in proportions of categorical variables and Mann-Whitney test was used for non-parametric distribution. The Pearson’s correlation coefficient was used to evaluate the presence of significant differences between group means. The Pearson’s correlation coefficient was used to evaluate the presence of significant differences between group means. The Pearson’s correlation coefficient was used to evaluate the strength association between two variables. The level P < 0.05 was considered as the cut-off value for significance. Multivariate logistic regression analysis was performed.

**RESULTS**

Seventy-three patients out of 80 completed the study and follow up periods, and were classified into 2 groups: 38 patients received pegylated IFN and ribavirin (group A) and 35 received non-pegylated IFN and ribavirin (group B). Seven patients (2 in group A and 5 in group B) could not continue the study because of severe side effects or intolerance to treatment. Thyroid dysfunction in one patient in each group, intolerance of the drug’s side effect in another one in group A and in 2 patients from group B, in addition to increase of transaminases and thrombocytopenia in 2 patients with cirrhosis in group B were the causes of drug discontinuation. Male gender was predominant in both groups, 31 and 33 respectively. Baseline demographic data and disease characteristics were similar in both groups (Table 1). Thirty-one patients in group A and 30 in group B had a history of bilharziasis treated with either tarter emetic (44 patients) or praziquentel (17 patients). Among these, one had histological pattern of bilharzial granuloma in liver tissue, but none had active bilharziasis prior to treatment.

Patients who received pegylated IFN (29, 76.3%) showed a significant ETR in comparison to those receiving non-peg-IFN (14, 40%) (P < 0.002). A significant (P < 0.05) improvement in SR was noticed with Peg-IFN, where 25 patients in group A (65.8% of total number of patients who completed the study) and 9 (25.7%) in group B could retain negative viremia at the end of follow up period (Table 2). A significant negative correlation between age and sustained response was noted in both groups (P = 0.015) without a significant difference between both drugs. There was no correlation between gender, pre-treatment, viraemia or body weight and response rate (Table 3). There was a significant positive correlation between pretreatment ALT and ETR in patients receiving Peg-IFN but not in patients receiving IFN. Also, a significant positive correlation (P < 0.05) was found between stage of hepatic inflammation and response rate in patients treated with peg-IFN, but not with IFN (Table 3). Intent to treat (ITT) analysis showed significant improvement in both of ETR and SR with peg-IFN therapy, where ETR was 72.5% and 35%, respectively, while SR was 62.5% and 22.5% (P < 0.002).

Regarding viraemia, there was no significant difference between responders and non-responders in both groups and within the same group. Viral clearance after 12 wk of therapy was associated with high incidence of ETR and SR (P < 0.001), but also, without significant difference between both groups. By studying the relation between histopathological activity and response, treatment with peg-IFN showed a significant improvement in response and sustained response in patients with severe fibrosis (grade 3 and 4). Only one patient out of 11 with severe fibrosis showed ETR with conventional IFN therapy and unfortunately relapsed after discontinuation of treatment, while 8 patients out of 13 showed ETR with peg-IFN therapy and 5 of them could retain negative viremia at
72 wk (Table 4). There was no significant difference in response in bilharzial and non-bilharzial patients in both groups, where SR was achieved in 27 patients co-infected with bilharziasis (60.7%) and in 7 cases of HCV alone (58.3%) (Table 5).

With respect to safety and tolerability, peg-IFN was comparable to conventional IFN. Weight reduction was similar in both groups, where the mean reduction was 2.9 ± 4.3 kg and 2.6 ± 2.7 kg respectively. After flu-like picture, hematological side effects represented the commonest encountered problem (Table 6). Although anemia was seen in 71.1% and 65.7% in both groups respectively, only 39.5% and 37.1% in both groups developed Hb drop more than 30 mg/L or > 30% of baseline level and required growth stimulating factors (These figures were related only to those patients who completed the study). Two patients from group B with cirrhotic changes were withdrawn because of thrombocytopenia. The proportions of patients withdrawn from treatment because of laboratory abnormalities or other adverse effects were similar in both groups and no new or unexpected adverse effects specific to peginterferon were presented. On multivariate logistic regression analysis, no significant predictive values were noted.

**DISCUSSION**

Hepatitis genotype is now recognized as the most important baseline characteristic determining treatment regimen and the most useful predictor of response\[^{[14]}\]. Slow viral dynamics, particularly second-phase decay\[^{[15]}\] and limited effectiveness of IFN in blocking the virion have been implicated in poor response to IFN therapy in hepatitis C genotype 4 patients\[^{[16]}\], which genotype has been described as a difficult-to-treat one. Unfortunately, this is the predominant genotype in the Middle East where large numbers of affected individuals are reported. A great improvement in response has recently been noted in all genotypes after the introduction of pegylated forms of IFN, whether as monotherapy or combined with ribavirin. Data presented in this study further reinforce the superior efficacy of PegIFN/Ribavirin combination therapy in terms of ETR and SVR in HCV genotype 4 infection. This is in accordance with earlier reports (Thakeb\ et al\, 2004\[^{[17]}\]; Shobokshi\ et al\, 2004\[^{[18]}\]; and Diago\ et al\, 2004\[^{[19]}\]). The lower SR noted compared to that reported by Diago\ et al\, for western genotype 4 cases (65.8% vs 79%) may reflect a difference in sensitivity of genotype 4 subtypes to PegIFN-α2a. The improved response to PegIFN-α2a in genotype 4 compared to conventional IFN and PegIFN-α2a previously reported by us\[^{[20,21]}\] can be attributed, at least in part, to a high and persistent trough serum level of PegIFN-α2a in the first 4 wk of treatment which led to rapid viral eradication\[^{[22,23]}\], or the recently reported third phase decay with PegIFN-α2a in the first 1-4 wk of therapy\[^{[24]}\]. Other causes also include

---

**Table 3** Comparison between responders and non-responders in both hepatitis C groups (mean ± SD)

| Variable                  | Group A (PEG-IFN+RBV) n = 38 | Group B (IFN+RBV) n = 35 |
|---------------------------|-------------------------------|---------------------------|
|                          | R1                            | NR1                       | SR1                        |
| Age (yr)                  | 44.7 ± 5.4                    | 47.8 ± 7.9                | 44.2 ± 5.8                 |
|                           | Group B (IFN+RBV) n = 35      |                           |                           |
| Body mass (kg)            | 82.6 ± 10.2                   | 79.7 ± 17.0               | 82.7 ± 9.8                 |
|                           | Before treatment              |                           |                           |
| ALT (μkat/L)              | 2.559 ± 1.564                 | 1.524 ± 0.082             | 2.757 ± 1.607              |
|                           | After 3 mo                    | 1.065 ± 0.980             | 1.084 ± 1.039              |
| Baseline HCV RNA (MU/L)   | 473.934 ± 373.542             | 496.256 ± 667.356         | 472.444 ± 402.109          |
|                           | 312.786 ± 185.583             | 361.857 ± 339.942         | 346.667 ± 207.364          |

---

**Table 4** Comparison of response in both hepatitis C groups according to histopathological changes n (%)

| Variable                  | n   | Responders | Non responders | Among responders |
|---------------------------|-----|------------|----------------|-----------------|
|                           |     | SR         | NR             | Sustained response | Relapse |
| Severe Fibrosis           |     |            |                |                  |         |
| A1                        | 13  | 8 (61.5)   | 5 (38.5)       | 5 (62.5)         | 3 (37.5) |
| B1                        | 11  | 1 (9.1)    | 10 (90.9)      | 0 (0.0)          | 1 (100.0) |
| Mild fibrosis             |     |            |                |                  |         |
| A1                        | 25  | 21 (84.0)  | 4 (15.0)       | 20 (95.2)        | 1 (4.8)  |
| B1                        | 24  | 13 (54.2)  | 11 (45.8)      | 9 (69.2)         | 4 (30.8) |
| Severe inflammation       |     |            |                |                  |         |
| A1                        | 31  | 22 (71.0)  | 9 (29.0)       | 18 (81.8)        | 4 (18.2) |
| B1                        | 27  | 7 (25.9)   | 20 (74.1)      | 4 (57.1)         | 3 (42.9) |
| Mild inflammation         |     |            |                |                  |         |
| A1                        | 7   | 7 (100.0)  | 0 (0.0)        | 7 (100.0)        | 0 (0.0)  |
| B1                        | 8   | 7 (87.5)   | 1 (12.5)       | 5 (71.4)         | 2 (28.6) |

---

\[^{[1]}\] Responders; \[^{[2]}\] Non responder; \[^{[3]}\] Sustained response.
In agreement with Tsubota et al[31], we could not find any correlation between pretreatment viral load and SR, which implies that HCV-RNA levels per se are less influential compared to the major impact of genotype that generally determines the rate of SR.

HCV patients co-infected with schistosomiasis exhibited a unique clinical, virological and histological pattern manifested by an increased incidence of viral persistence with high HCV-RNA titers and accelerated fibrosis. This may be attributed to the fact that patients with schistosomiasis have a down regulated immune response to HCV in the form of reduced IFN-α, IL-4 and IL-10 secreted by HCV-specific T cells[33]. In spite of this, we did not find any significant difference in response to either IFN forms in cases of combined infections. This might be explained by the recent observation of El Rafei and colleagues[34] that Schistosoma mansoni by targeting a specific subset of memory CD8 cells, reduces the late differentiated memory T cell population in HCV co-infected individuals. This implies that patients infected with the genotype 4 can still mount HCV-specific T cell responses, despite the prevalence of concomitant schistosomiasis.

As for safety and tolerability, both IFN forms were comparable. As in previous reports, anemia and thrombocytopenia were the commonest haematological adverse events of the combination therapy[35]. The latter effect was not demonstrated in our patients and 4 had to discontinue treatment in the first 12 wk. Adherence to therapy is increasingly recognized as a key determinant in the outcome of antiviral therapy in chronic hepatitis[36] and although erythropoietin stimulates both erythropoiesis and thrombopoiesis[37], the latter effect was not demonstrated in our patients and 4 had to discontinue treatment because of thrombocytopenia.

We can conclude that concomitant HCV-genotype 4 and bilharzial infections do not seem to affect the improved responses achieved with pegylated interferon α2a plus ribavirin combination therapy. Also, in spite of the improved response in advanced fibrosis and compensated cirrhosis, advanced histopathological changes, coupled with positive viremia after 12 wk of

The significant correlation noted in the present study between viral clearance at wk 12 and SVR, regardless of the type of IFN used, confirms a consistent relationship between the rapidity of HCV-RNA suppression and the likelihood of achieving SR[25,26]. Conversely, patients showing positive PCR at wk 12, all failed to achieve SR regardless of ETR seen in 2 of them. This suggests that a positive PCR at wk 12 in genotype 4 cases might be considered as a strong negative predictor of response.

In terms of pretreatment predictors, only patient's age showed a negative correlation with response rate. This is probably not related to age per se, but rather to the age of infection, or in other words, the duration of infection, since older patients are known to develop a higher rate of liver fibrosis[27]. The presence of cirrhosis has been shown to be independently associated with decreased SVR in HCV infected patients[28]. In this respect we could demonstrate a superior SR with PegIFN-α2a over non-pegylated IFN (25.7% vs 0%) in both advanced fibrosis and compensated cirrhosis genotype 4 patients. Similar results were reported by Heathcote et al in 2000[29] and Marcellin et al in 2004[30].

In agreement with Tsubota et al[31] and contrary to Picciotto et al[32], we could not find any correlation between pretreatment viral load and SR, which implies that HCV-
therapy, still remain the most important negative predictive factor for response in genotype 4 patients. A non-stop and extensive work is still needed to win the battle against HCV. Each new pharmacological modification carries with it more hope for better control of this complicated disease and tells that the difficult to treat genotype 4 will eventually be conquered.

REFERENCES
1. Farci P, Purcell RH. Clinical significance of hepatitis C virus genotypes and quasispecies. Semin Liver Dis 2000; 20: 103-126
2. Lyra AC, Ramakrishnan S, Bacon BR, Di Bisceglie AM. Infection with hepatitis C virus genotype 4 in the United States. J Clin Gastroenterol 2004; 38: 68-71
3. El-Zayadi A, Simmonds P, Dabbous H, Prescott L, Selim O, Ahdy A. Response to interferon-alpha of Egyptian patients infected with hepatitis C virus genotype 4. J Viral Hepat 1996; 3: 261-264
4. Shobokshi O, Serebour FR, Skakni L, Al Jaser N, Tantawe Shobokshi OA, Serebour FE, Skakni L, et al. Combination therapy of peginterferon alfa-2a (40KD) (Pegasys®) and ribavirin (Copegus®) significantly enhance sustained virological and biochemical response rate in chronic hepatitis C genotype 4 patients in saudi arabia. Abstract. Hepatology 2003; 38: 636A
5. Diago M, Hadziyannis S, Bodenheimer H, Hassanein T, Uchman S, Marcellin P, Ramadori G, Delwaide J, Sedanati F. Optimized Virological Response In Patients With Genotype 4 Chronic Hepatitis C Treated With Peginterferon Alfa-2a (40KD) (Pegasys®) In Combination With Ribavirin (RBV). Abstract. Hepatology 2002; 36: 364A
6. Derbala M, Omar M. Efficacy of interferon therapy for hepatitis C virus in patients with schistosomiasis. results from a comparative study. Ksar Al Ain Med J 1998; 4 Suppl 1: 247-254
7. Derbala M, Amer A, Bener A, Lopez AC, Omar M, El-Zayadi A. Treatment of HCV with peginterferon and ribavirin 2b-ribavirin combination in Egyptian patients with genotype 4 chronic hepatitis. J Viral Hepat 2005; 12: 380-385
8. Foster GR. Review article: pegylated interferons: chemical and clinical differences. Aliment Pharmacol Ther 2004; 20: 825-830
9. Di Bisceglie A, Rustgi V, Thuluvath P, Davis M, Ghali R, Lyons M, Ondovik M, Lopez-Talaveria J, Hamzeh F. Pharmacokinetics and pharmacodynamics of pegylated interferon-alpha2b-ribovirin combination in Egyptian patients with genotype 4 chronic hepatitis. J Viral Hepat 2005; 12: 425-433
10. Kamal SM, El Tawil AA, Nakano T, He Q, Rasenack J, Hakam SA, Saleh WA, Ismail A, Aziz AA, Madwar MA. Peginterferon [alpha]-2b and ribavirin therapy in chronic hepatitis C genotype 4: impact of treatment duration and viral kinetics on sustained virological response. Gut 2005; 54: 858-866
11. Ticehurst J, Hu S, Hamzeh F, Thomas D. Factors affecting hcv viral load in patients with genotype 1 infection (Abstract 411). Hepatology 2004; 40 Suppl: 342A
12. Al-Faleh FZ, Aljumah A, Rezeig M, Al-Kanawi M, Alahdal M, Al-Humayed S, Mayet I, Al-Juhani M, Al-Karawi M, George K, Sheib F. Treatment of chronic hepatitis C genotype IV with interferon-ribavirin combination in Saudi Arabia: a multicentre study. J Viral Hepat 2000; 7: 287-291
13. Heathcote EJ, Shiffman ML, Cockrell WG, et al. Peginterferon alfa-2a in patients with chronic hepatitis C and cirrhosis. N Engl J Med 2000; 343: 1673-1680
14. Marcellin P, Roberts S, Alberti A, Trepo C, Zeuzem S, Hoel Sette Jr, Brouwer J. Sustained virological and biochemical response to peginterferon alfa-2a plus ribavirin in patients with chronic hepatitis C and compensated cirrhosis/bridging fibrosis. Hepatology 2004; 40: 531A
15. Tsubota A, Arase Y, Someya T, Suzuki Y, Suzuki F, Saitoh S, Ikeda K, Akuta N, Housa T, Kobayashi M, Kumada H. Early viral kinetics and treatment outcome in combination of high-dose interferon induction vs. pegylated interferon plus...
32 Picciotto A, Campo N, Brizzolara R, Sinelli N, Poggi G, Grasso S, Celle G. HCV-RNA levels play an important role independently of genotype in predicting response to interferon therapy. *Eur J Gastroenterol Hepatol* 1997; 9: 67-69

33 El-Kady IM, Lotfy M, Badra G, El-Masry S, Waked I. Interleukin (IL)-4, IL-10, IL-18 and IFN-gamma cytokines pattern in patients with combined hepatitis C virus and Schistosoma mansoni infections. *Scand J Immunol* 2005; 61: 87-91

34 Elrefaei M, El-sheikh N, Kamal K, Cao H. Analysis of T cell responses against hepatitis C virus genotype 4 in Egypt. *J Hepatol* 2004; 40: 313-318

35 Dieterich DT, Spivak JL. Hematologic disorders associated with hepatitis C virus infection and their management. *Clin Infect Dis* 2003; 37: 533-541

36 Patel K, Anouk T. Adherence to antiviral therapy in chronic hepatitis. *Current hepatitis reports* 2004; 3: 10-15

37 Homoncik MG, Sieghart W, Formann E, Schmid M, Ferlitsch A, Ferenci P, Gangl A, Jilma B, Peck-Radosavljevic M. Erythropoietin and platelet counts, platelet function in patients with chronic hepatitis C undergoing combination antiviral therapy : a randomized, placebo-controlled, double-blind study (Abstract 527). *Hepatology* 2004; 40 suppl 1: 392A