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Early Virological Response of the First Line Combination Therapy (Pegylated Interferon α - 2a and Ribavirin) in Iraqi Chronic Hepatitis C Patients and Their Psychological Adverse Effects

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I. Introduction

The hepatitis C virus (HCV) is a major public health problem and a leading cause of chronic liver disease (Williams R, 2006). Hepatitis C is the principal cause of death from liver disease and the leading indication for liver transplantation in the United States (Kim W, 2002).

Approximately 20-30% of patients with chronic HCV infection progress to end stage liver disease within 20 years and a small percentage develop hepato-cellular carcinoma (Walker R and Edwards O, 2007). HCV infection is now the leading worldwide indication for liver transplantation (Ryan K and Ray C, 2004, Walker R and Edwards O, 2007).

First-line treatment for HCV includes pegylated interferon plus ribavirin. The dosing regimen varies with the specific product and the duration of therapy varies with the product and HCV genotypes (Wells B *et al*, 2006).

Interferon (IFN) was first described in 1957 as an antiviral compound in chick embryo cells (Greenwood D *et al*, 2007). Its efficacy for treatment of HCV first was recognized when Hoofnagle *et al* (1986) published a preliminary findings when HCV was known as non-A, non-B hepatitis (Sangik O and Afdhal N, 2006). The United States Food and Drug Administration (FDA) approved alpha interferon monotherapy for the treatment of chronic HCV infection in 1992. Ribavirin was approved for use as an adjunct to interferon therapy of hepatitis C in 1998. Pegylated forms of interferon in combination with ribavirin were approved in the United States in 2001 (Hoofnagle J, 2009). There are two licensed pegylated interferons, peg interferon α-2b (Peg-Intron, Schering Plough Corp.), with a 12-kd linear polyethylene glycol (PEG) covalently linked to the standard interferon α-2b molecule, and peg interferon α-2a (Pegasys, Hoffmann-La Roche) with a 40-kd branched PEG covalently linked to the standard interferon α-2a molecule (Zeuzem S *et al*, 2003). The doses of these two forms of pegylated interferons (Peg IFNs) differ (Ghany M *et al*, 2009). Peg IFN α-2b is dosed according to body weight (1.5 μg/kg once weekly), while the larger Peg IFN α-2a is given in a fixed dose of 180 μg once weekly (Cornberg M *et al*, 2002). Peg IFN α-2b may also be dosed at 1.0 μg/kg once patients become negative for HCV-RNA without major declines in sustained virological response (SVR) rates (McHutchison J *et al*, 2009, Manns M *et al*, 2011).

Pegylation of interferons increases the persistence of the interferon in the blood, extend half life, better toleration and much importantly produces much superior virological response (Greenwood D *et al*, 2007).

The two licensed peginterferons have been shown in head-to-head comparison to be equivalent in efficacy and to have similar safety profiles (McHutchison J *et al*, 2009). Although smaller trials from southern Europe have suggested slightly higher SVR rates in patients treated with Peg IFN α-2a (Ascione A *et al*,

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2010, Rumi M *et al*, 2010), a large US multicentre study did not detect any significant difference between the two Peg IFNs in combination with ribavirin (RBV) regarding SVR (McHutchison J *et al*, 2009).

Ribavirin is a synthetic nucleoside in which ribose is linked to a triazole derivative. Like other nucleoside analogues it has to be activated intracellularly by phosphorylation (Greenwood D *et al*, 2007). The precise mode of action has proved elusive, though there are several theories including the possibility that it causes lethal mutations in viral nucleotides (Greenwood D *et al*, 2007). Ribavirin has limited utility as monotherapy and should be administered twice daily with food when used in combination with α-interferons (DiPiro J *et al*, 2005).

Meta-analyses and systematic reviews confirm that a combination of PegIFN with RBV is effective in treating patients with chronic hepatitis C (CHC), leading to high levels of SVR (Strader D *et al*, 2004). In general, the combination of RBV with α-interferons is associated with numerous adverse events to multiple organ systems, and these should be discussed with patients prior to initiation of therapy (DiPiro J *et al*, 2005).

This study was designed to measure early virological response (ERV) in HCV infected patients receiving first line combination therapy (Peg interferon α-2a and ribavirin) and to evaluate response according to different doses of ribavirin but fixed dose of peg interferon α-2a. Also this study was conducted to monitor appearance of psychological adverse effects to guide the patients and provide necessary instructions.

II. Subjects and Methods

a) Patients

This study was conducted during the period from the 15th March 2012 till 1st October 2012, which was carried out in Gastro-enterology center at General teaching hospital in Sulaimania city. Fifty six patients (30 males and 26 females) with an age of 18-70 years were divided into three groups according to viral genotypes (36 patients infected with genotype 1 and 20 patients infected with genotype 4), dose of the ribavirin and body weight of the patients. Throughout the study period, six patients were lost (4 males and 2 females) and only fifty patients (26 males and 24 females, in whom 32 patients were infected with genotype 1 and 18 patients with genotype 4) followed up. Four of the six patients stopped taking the drug (poor adherence), one female died (car accident), and the other female withdraw the drug after one month of treatment because of severe dehydration, arthralgia, myalgia, head ache, nausea and vomiting. All patients were recieving combination of 180 μg/week of Peg IFN α-2a s.c. injection (Pegasys® by Roche pharmaceutical company, Switzerland) and different doses of ribavirin capsules (Rebetol® by Schering pharmaceutical company, USA).

For monitoring of hematological and other common adverse effects from combination therapy that may necessitate dose adjustment or even withdrawal of the drugs, the patients were examined weekly for the first month then monthly for the other 2 month.

Ethical authorization and permission were submitted from each of college of pharmacy, directory of health and gastroenterology center in Sulaimania city. Informed concern had been taken from patients studied.

The previously diagnosed patients were recruited into the following prospective groups:

Group A : This group included fourteen patients infected with HCV genotype one, 10 males and 4 females ranging 22-65 years (mean ± SD, 45.4 ± 12.15), with body weights more than 75 kg, taking combination of PegIFN α-2a 180 μg once weekly as subcutaneous injection and RBV capsule 1200 mg per day (three 200 mg capsules after breakfast and three 200 mg capsules after dinner).

Group B : Included eighteen patients infected with HCV genotype one, 9 males and 9 females ranging 21-67 years (44.94 ± 14.7), with body weights equal or less than 75 kg, taking combination of Peg IFN α-2a 180 μg once weekly as subcutaneous injection and RBV capsule 1000 mg per day (three 200 mg capsules after breakfast and two 200 mg capsules after dinner).

Group C : Included eighteen patients infected with HCV genotype four, 7 males and 11 females ranging 18-65 years (43.78 ± 13.28), taking combination of Peg IFN α-2a 180 μg once weekly as subcutaneous injection and RBV capsule 800 mg per day (two 200 mg capsules after breakfast and two 200 mg capsules after dinner).

b) Healthy Subjects

Twenty healthy individuals were involved as a control group, including 8 males and 12 females ranging 19-69 years (39.1 ± 13.4).

c) Inclusion criteria

- Patients confirmed to have HCV infection, genotypes 1 and 4.
- Patients between 18-70 years old of both genders.
- Treatment naïve patients.
- Patients willing to be treated and to adhere to treatment requirement.

d) Exclusion criteria

- Patients with HIV or HBV co-infection.
- Patients with solid organ transplantation (heart, lung, liver, and kidney)
- Patients with decompensated liver disease.
- Patients allergic to any one of the components of combination therapy.
- Difficult to follow up patients (alcoholics, patients who travel frequently).
- Breast feeding and pregnancy or patients unwilling to comply with adequate contraception.

- Patients with thalasemia, cytopenia, or severe anemia.
- Patients with renal failure.
- Patients with severe psychiatric disorder.
- Patients with severe immunosuppresion.
- Patients with heart failure or significant coronary or CVD.
- Patients with untreated thyroid disease.
- Patients with unknown HCV genotype (refused to do viral genotyping).

e) Sample collection and preparation

4 ml of venous blood was collected from each patient. The blood was drawn by venipuncture under basal condition using tourniquet with vacationer system, then centrifuged at 3000 rpm to seperate plasma and stored in ACD or EDTA tube and freezed at -20 ℃ (within 4 hrs of collection) and analyzed within 2 week. The assessments were done twice for each patient, once before starting treatment and second time three months after starting treatment with combination therapy of peg IFN α-2a and RBV.

f) Sample processing and extraction

Purification of viral nucleic acid from cell was carried out using genomic DNA extraction method in which nucleic acids of the virus are lysed quickly and efficiently using lyses buffer which is a highly concentrated solution of chaotropic salt. When combined with ethanol, the buffer creates optimum conditions for nucleic acid binding to the glass fiber matrix of the column tube. Contaminants such as salts, metabolites and soluble macromolecular cellular component are removed in the washing step. Nucleic acid is eluted in RNAase-free water and is then ready for use in subsequent reactions including real time RT-PCR and other enzymatic reactions (Bioneer Inc., 2009).

g) Amplification of viral nucleic acid

Amplification of viral nucleic acid (RNA for HCV) was carried out by real time RT-PCR procedure using EXICYCLER® (BIONEER/ South Korea). RNA templates are first reverse-transcribed to generate complementary cDNA strands followed by a DNA polymerase-mediated cDNA amplification. DNA detection simultaneous to amplification is preferentially achieved by the use of target sequence-specific oligonucleotides linked to two different molecules, a fluorescent reporter molecule and a quenching molecule. These probes bind the target cDNA between the two PCR primers and are degraded or released by the DNA polymerase during DNA synthesis. In case of degradation the reporter and quencher molecules are released and separated, which results in the emission of an increased fluorescence signal from the reporter. The fluorescence signal, intensified during each round of amplification, is proportional to the amount of RNA in the starting sample (Mauss S *et al*, 2012).

h) Psychological evaluations

For evaluation of psychological conditions of HCV infected patients before treatment and three months after starting treatment with 180 μg/week of s.c. peg IFN α-2a and different doses of RBV, each patient were interviewed and filled a used questionnaire. The questionnaire was prepared by a psychologist Dr. Rebwar H. Gharib at 2008 for his research (Gharib R, 2008) using DSM-IV scoring system (American Psychiatric Association, 1994). According to the questionnaire, patients who presented with at least 5 of depressive symptoms during the same two-week period or more, at least one of which is either depressed mood or loss of interest, is considered to have major depression. Patients who presented with at least 3 of depressive symptoms during the same two-week period or more, at least one of which is either depressed mood or loss of interest, is considered to have minor depression. Insomnia, suicidal idea and suicidal attempt were also considered separately.

i) Statistical analyses

All data are represented as mean ± standard error of means (SEM). Statistical analysis were carried out using paired sample T-test to compare treatment groups, focusing on changes from pre-treatment values and after three months of starting treatment of each group. Statistical analyses were carried out using SPSS 16.

III. Results

a) Effects of combination therapy on viral load

Table (1) and figure (1) show a significant reduction in viral load (amount of HCV-RNA in serum) three months after starting treatment compared to viral load before starting treatment. Nearly in all patients (47 patients), the viral load became no detectable in serum, but in only two patients (one 38 years old female, and one 36 years old male, both in group C) the virus was still detectable but comparing to pre-treatment amount there was more than two log reduction. Only one 63 years old female in group B was resistant to treatment and viral load increased by 2 times the pre-treatment value three months after starting treatment. In those patients whose serum viral RNA became no detectable, viral load reduced to 0.0 ± 0.0 IU/ml compared to pre-treatment values of 19427000 ± 527847 IU/ml (very high), 2374000 ± 331629 IU/ml (high), 914420 ± 31540 IU/ml (moderate) and 258500 ± 20169 IU/ml (low) with percent reduction of 100% .

b) Other parameters

In all three groups (as showed in tables 2 and 3), there were significant reductions ($p < 0.05$) in the levels of each of hemoglobin (Hb), white blood cell count (WBC), absolute neutrophil count (ANC), platelet count (PLT), random plasma glucose level, Alanine

aminotransferase (ALT), Alkaline phosphatase (ALP), serum albumin and body weight three months after starting treatment compared to pre-treatment values. Neither dose reduction nor pharmacological interventions were required, since hematological reductions were not severe.

c) Psychological condition

In figure 2 for group A patients (n=14); before starting treatment, two patients (one male and one female) were complaining from isolated insomnia (insomnia alone, without any other psychological symptoms), which represents 14.3% of all group A patients, who both became suffering from major depression later three months after starting treatment. And one female patient was complaining from minor depression before treatment representing 7.1% of all the group's patients who also became suffering from major depression three months after starting treatment. The remaining 78.6% were psychologically normal patients. After 3 months of starting treatment with s.c. Peg IFN α-2a 180 μg/week and RBV 1200 mg/day, three cases (21.4%) of minor depression, four cases (28.6%) of major depression one of whom also had suicidal idea, three cases (21.4%) of isolated insomnia were reported. Among those who reported major depression, one patient was male (who also had a suicidal idea) and the other three were females, all three patients with minor depression were male, and those with isolated insomnia were two males and one female. Overall, three months after starting treatment, only four patients (28.6%) were not complaining from psychiatric symptoms (three males and one female), while the remaining ten patients (71.4%) were complaining from psychiatric symptoms as individualized above.

In figure 3 for group B patients (n=18); before starting treatment, six patients (one male and five females) were complaining from minor depression which represents 33.3% of all group B patients, one female of whom had suicidal idea. Later, three months after starting treatment, all of these six patients became suffering from major depression, two females of these became having suicidal idea without suicidal attempt. And only one female patient representing 5.6% was complaining from isolated insomnia, who became majorly depressed and died later after three months of starting treatment as a result of suicidal attempt. The remaining 61.1% were psychologically normal patients. After 3 months of starting treatment with s.c. Peg IFN α-2a 180 μg/week and RBV 1000 mg/day, seven cases (38.8%) of minor depression, five cases (27.8%) of major depression three of whom had suicidal idea, three cases (16.7%) of isolated insomnia were reported. Unfortunately, 5 days after my interview with patients, one 43 years old female who had isolated insomnia alone before starting treatment, committed suicide by jumping out of a building, after three days of staying at hospital, she passed away. One point of note is that, this female had experienced major depression and frequent suicidal idea compared to the pre-treatment state, before committing suicide. Among those who reported major depression, two patients were male and the other three were females, two males and five females were with minor depression, and those with isolated insomnia were two males and one female. Overall, three months after starting treatment, only three patients (16.7%) were not complaining from psychiatric symptoms, while the remaining fifteen patients (83.3%) were complaining from psychiatric symptoms as individualized above.

In figure 4 for group C patients (n=18); before starting treatment, two female patients were complaining from minor depression which represented 11.1% of all group C patients, one of them was also complaining from suicidal idea. One female (5.6%) was complaining from major depression before treatment who interestingly became minor depressed three months after starting treatment. No one was complaining from isolated insomnia before treatment. The remaining 83.3% were psychologically normal patients. After 3 months of starting treatment with s.c. Peg IFN α-2a 180 μg/week and RBV 800 mg/day, four cases (22.2%) of minor depression, five cases (27.8%) of major depression one of whom had suicidal idea and tried to commit suicide, four cases (22.2%) of isolated insomnia were reported. Unfortunately, three days before my interview with patients, one 54 years old female who already had minor depression and suicidal idea even before starting treatment, tried to commit suicide by burning herself, but she was lucky and rescued by her son who prevented her from doing such a thing. One point of note is that, at the time of interview, three days before trying to commit suicide, this female had experienced major depression and more frequent suicidal idea compared to the pre-treatment state. Among those who reported major depression, one patient was male and the remaining four were females, two males and two females were with minor depression, and those with isolated insomnia were two males and two females. Overall, three months after starting treatment, only five patients (27.8%), two males and three females, were not complaining from psychiatric symptoms, while the remaining thirteen patients (72.2%) were complaining from psychiatric symptoms as individualized above.

In figure 5 for control group (n=20); Two patients (one male and one female) were complaining from minor depression which represents 10% of all control group individuals, one female with major depression and suicidal idea which represents (5%), and seven patients (two males and five females) representing 35% were complaining from isolated insomnia, the remaining 50% were psychologically normal individuals.

Finally in figure 6 we may say that, among all three groups of patients (A, B, and C), percent of patients experienced major depression and percent of those who were psychologically normal three months after starting treatment, were greater in group A (28.6% for each) compared to group's B and C patients. For minor depression, the percent of patients experiencing it, was greater in group B patients (38.8%) compared to other groups, and isolated insomnia was more frequent among group C patients than group A and B patients, and percent of patients experienced major depression were the same in both groups B and C (27.8%). One point of note, percent of individuals experiencing isolated insomnia was greater (35%) among control group than other three patient groups after three months of treatment.

IV. Discussion

Hepatitis C virus infection is still a global and the possible new approaches for conquering the health care challenges. The standard of care (SOC) therapy for patients with chronic hepatitis C virus infection has been the use of both peg interferon and ribavirin (Ghany M *et al*, 2011). These drugs are administered for either 48 weeks (HCV genotypes 1, 4, 5, and 6) or for 24 weeks (HCV genotypes 2 and 3), inducing sustained virological response rates of 40%-50% in those with genotype 1 and of 80% or more in those with genotypes 2 and 3 infections (Manns M *et al*, 2001, Fried M *et al*, 2002a, Hadziyannis S *et al*, 2004). Although PegIFN and RBV remain vital components of therapy, the emergence of direct acting antivirals has led to the concept of triple therapy in many patients with genotype 1 chronic HCV infection (Ghany M *et al*, 2011).

The therapy of hepatitis C began almost 26 years ago with a small trial of recombinant human interferon alfa (Hoofnagle J *et al*, 1986). The rationale for using interferon was its broad antiviral effects and the suspicion that it might be active against the still-undiscovered agent of non-A non-B hepatitis. Not until the discovery of the HCV, at 1989 (Feitelson M, 2003), were the effects of interferon understood. Nevertheless, interferon was approved for use for hepatitis C treatment in the United States in 1992 (Hoofnagle J, 2009).

The second important advance in hepatitis C therapy came with the use of ribavirin. Ribavirin was approved for use as an adjunct to interferon therapy of hepatitis C in 1998. A third advance in therapy of hepatitis C came soon thereafter, with the introduction of pegylated forms of interferon that allowed for once-weekly (rather than thrice-weekly) injections. Peg nterferon was approved in the United States in 2001 (Hoofnagle J, 2009). The treatment paradigm for HCV has changed with the recent FDA approval of two first generation protease inhibitors, telaprevir, and boceprevir for genotype 1 infected individuals. Nonetheless, ribavirin and pegylated interferon remain integral components of treatment (Ghany M *et al*, 2011).

In our community, combination of peginterferon and ribavirin is still the first choice because of high cost of triple therapy and difficulties in providing these drugs on continuous bases. Despite that, majority of our patients cannot afford such a large amount of money for providing the drugs themselves continuously. So in order to determine advantage and effectiveness of this first line combination therapy (by measuring early virological response which is a main predictor for sustained virological response in majority of patients) in HCV infected patients in our communuity, its psychological effects after three months of treatment, present study has been conducted.

The results of present study are somewhat conflicting and out of line with the results of other studies because patients treated in clinical trials, represent a highly selected population not necessarily representing general HCV infected population (Ferenci P *et al*, 2005). Therefore, it is not clear if the reported efficacy and safety of peg interferon α and ribavirin regimen would be validated in routine clinical practice.

Response to standard treatment with peg interferon α-2a and ribavirin in patients with chronic hepatitis caused by HCV, including genotypes 1 and 4, has been widely studied and documented in numerous populations (Fried M *et al*, 2002a, Hadziyannis S *et al*, 2004). Approximately 80% of patients who have genotype 1 and virtually all patients who have genotypes 2 and 3 achieve an early virological response (Davis G, 2002, Fried M *et al*, 2002a, Lindsay K, 2002, Shiffman M *et al*, 2007a).

Early virologic response (EVR) was defined as the > 2 $\log_{10}$ reduction in HCV RNA in serum 12 weeks after starting treatment. In case of total absence of HCV RNA in serum 12 weeks after starting treatment, a complete early virologic response (cEVR), which is a more promising predictor of sustained virological response (SVR) than EVR, is obtained (Mauss S *et al*, 2012). Over all, in this study among all participants, 94% achieved cEVR (100%, 94.4% and 88.9% for groups A, B and C respectively) 4% achieved > 2 $\log_{10}$ reduction in HCV RNA, i.e., EVR (11.1% of group C patients) and 2% null responder (5.6% of group B patient) who discontinued drugs after 12 weeks of starting treatment after confirming increased viral load, patient's instruction and acceptance.

In a retrospective analysis done by Gheorghe L *et al* (2005) in Romania that consisted of 174 HCV infected patients, therapy was stopped in patients who do not achieve 2 log reductions in viral load 12 weeks after starting treatment, the same strategy that followed in present study.

Early virological response (EVR) in a clinical trial at Beth Israel Medical Center NY (Johnson T *et al*, 2004) was 63% in genotype1 patients treated with peg interferon α-2a and ribavirin. This difference in present study results from that in Beth's, may be explained by

more advanced illness and a high proportion of black patients in Beth's study.

In one of a phase III trials of peg interferon α-2a and ribavirin, by week 12 of therapy, EVR was achieved by 86% of patients (Fried M *et al*, 2002a) which is near to present study results. These results suggest that patients who have EVR who remain PCR positive at 12 weeks (not complete absence of HCV RNA) should have PCR testing repeated after 24 weeks before making any decision about discontinuing therapy. Achievement of EVR can provide a goal to motivate patient adherence during the first months of therapy, and early testing provides the opportunity to reassess the need for continued treatment. Consequently, when an EVR is absent, discontinuation of therapy should be considered because the likelihood of sustained response is negligible, but the decision must be made on an individual patient basis. If uncertainty exists, retesting should be considered before stopping therapy (McHutchison J and Fried M, 2003, Manns M, 2004), which was the case with the female patient in group B in this study, when repeated viral load testing after one week of last PCR showed the same increase in HCV RNA compared to baseline level.

In a study done by Ascione A *et al* (2010) in Italy including both genotypes 1 and 4, EVR was obtained in 85% of all patients. The majority of patients obtained a complete EVR, while the number of those who obtained a partial EVR was only 8.8%. The results of Ascione A *et al*'s study are nearly the same as that in present study.

In the registration trials of peg interferon α-2a plus ribavirin, 10% to 14% of patients had to discontinue therapy due to an adverse event (Manns M *et al*, 2001, Fried M, 2002b), compared to 2% discontinuation in present study. Laboratory abnormalities are the most common reasons for dose reduction. Among these, neutropenia (absolute neutrophil count [ANC] of 1500 mm^3) was a frequent laboratory abnormality, occurring in 18% to 20% in the two large phase III clinical trials where the dose was reduced 50% for an ANC of 750 mm^3 and permanently discontinued for an ANC of < 500mm^3 (Manns M *et al*, 2001, Fried M *et al*, 2002a). Severe neutropenia, ANC <500 mm^3, occurred in 4% of subjects. None of these lab abnormalities were reported in present study participants. Actually these abnormalities happened in participants but not so severe to necessitate dose reduction but if study participants were followed up further (i.e., more than three months) these severe effects that call for dose modification may appear. Interferon causes anemia via bone marrow suppression and ribavirin causes anemia via hemolysis (De Franceschi L *et al*, 2000).

For psychological presentation, among all 50 patients 28% presented with major depression 10% of whom had suicidal idea and 4% committed suicide. 28% presented with minor depression, 20% with isolated insomnia and the remaining 24% were psychologically normal HCV infected patients.

Major depression was more common in group a patients (28.6%) than group's B and C patients (27.8% for each group), minor depression was more common in group B patients (38.8%) than group A patients (21.4%) and group C patients (22.2%). Isolated insomnia was more common among group C patients (22.20%) as well as control group (35%) compared to group a patients (21.4%) and group B patients (16.7%). These results demonstrate that appearance of any type of depression or psychological symptoms is more related to individual's susceptibility for developing symptoms and surrounding environment, because as it obvious, all three groups of patients treated with equal doses of peg interferon α-2a but the percent of patients showed psychological presentations differ, and its known that it is interferon that induce psychological abnormalities not ribavirin, that's why psychological presentations in any one of the groups is not related to the variations in ribavirin dosing regimen. Only one interesting female patient in group C, who experienced major depression before starting treatment, became minorly depressed at 12th week of treatment. The pre-treatment depression in this patient was because of knowing that she is infected with HCV and misunderstood by some specialists that it is not curable and should be isolated from family and friends so as not to infect others. But later when we explained the disease course, routes of transmission and precautions that needed to be made, she felt better but still minor depressed after three months this one may be the effect of interferon on neurotransmitters.

Manns M *et al* (2006) demonstrated that depression in HCV-infected individuals occurs in up to 60**%** (Hilsabeck R and Malek A, 2004, Zacks S *et al*, 2006). During HCV treatment with interferon based regimens the prevalence of depression has been reported to be between 10%–40% depending on the screening method used (Zacks S *et al*, 2006). Recently, data from the Virahep-C study, a prospective analysis of depression during HCV genotype 1 treatment with peg interferon and ribavirin, demonstrated that low social support was independently associated with pre-treatment and on-treatment development of depression (Evon D *et al*, 2009). At any time during the Virahep-C study 20% had depressive symptoms whereas 18% of non-responders compared to 10% of responders had depression 6 months after the end of treatment, a difference that may be explained by the failure of a challenging 48-week treatment course. This explains that occurrence of depression is more common during first three months of treatment, the time when the patients are still unaware of their response rate to treatment. In Virahep-C study 21% of patients developed depression during the first 12 weeks, a result which is nearly the same as present study findings.

A recent study of 1010 HCV infected patients demonstrated that suicide risk was higher in males and in patients under the age of 45 (Kristiansen M *et al*,

2011), this finding is in contrary with that in present study, because the two patients who had suicidal idea and committed suicide (one died and the other one prohibited) were both females and the other three patients who had suicidal idea but did not try to commit it were 2 females and 1 male and all were above 40 years old. Different conclusions were reported in a study of almost 400 HCV-infected patients with genotype 1 on peg interferon and ribavirin, where just 3.5% reported suicidal ideation and none attempted suicide (Evon D *et al*, 2009), this may be due to extensive supervision and guidance of patients by psychiatrists and family involvement strategy but neither is done during present study period.

Elsewhere in the literatures, many HCV treatment studies have reported various depression and suicidal ideation rates, making the application of these results to clinical practice impractical. This inconsistency in reporting may reflect the utilization of different depression screening methods, physician and patient biases in diagnosing and reporting symptoms, and variable treatment protocols followed. It is important to acknowledge the effect of interferon on the thyroid and the potential development of depressive-like symptoms related to thyroid dysfunction, mimicking, or even masking depressive symptoms related to interferon use (Papafragkakis H *et al*, 2012).

In a cross-sectional study of 43 patients who had chronic hepatitis C and not receiving interferon α, Kraus M *et al* (2001) found several factors that correlated significantly with depression. Higher rates of depression were observed in older patients (>50 years; P = 0.024), in patients who were aware of their hepatitis diagnosis for more than 5 years (P = 0.003), and in patients who were informed that they were not eligible for interferon α therapy (P = 0.001). Furthermore, a lower incidence of depression was noted in patients who had been diagnosed with HCV recently (1–6 months; P = 0.003). If such evaluations were done in present study in HCV infected patients before starting treatment, at least some if not all explanations made by Kraus *et al* may be applicable especially age more than 50 years and newly diagnosed ones.

Finally we should not exclude the major role of patient care and need of clinical pharmacist interventions in improving patient's adherence and response to standard therapy. Interim results of a prospective, randomized, controlled multicenter study indicate that active intervention with patient education, aggressive side effect management, and expanded supportive nursing intervention with cognitive behavioral therapy by way of telephone calls for patients infected with HCV who are treated with Peg-IFN and RBV therapy is feasible, can decrease the dropout rate in the first 12 weeks of therapy, and is associated with significant improvements in patient quality of life at early time points in treatment (Sarrazin C et al, 2010a). In present study some if not all of mentioned above strategies followed, so this may be the main cause of high rate of EVR especially cEVR and low rate of unwanted effects of treatment on organ functions.

V. Conclusions

- First line combination therapy with Pegylated interferon α-2a and ribavirin is highly effective in early eradication of hepatitis C virus (98% EVR) in Iraqi chronic hepatitis C patients and can be used relatively safely .
- Lower doses of ribavirin lowers percent of patients who achieve complete EVR.
- Development of major depressive symptoms occurred frequently during Pegylated interferon α-2a and ribavirin treatment and was predicted by baseline depression scores and higher doses of ribavirin.
- Patient care, patient instruction by clinical pharmacist and family involvement strategies have a great role in improving adherence, minimizing early drug withdrawal, managing mild unwanted disturbing effects and help minimizing unwanted psychological effects.

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Table 1 : Viral load (amount of HCV RNA in serum in IU/ml) of HCV infected patients, genotypes one and four, before treatment and 3 months after starting treatment with PegIFN α-2a 180 μg/week and RBV 1200, 1000 or 800 mg/day. Each value represents the mean ± standard error. Number of patients = 47 (Very high viral load=13, High viral load=15, Moderate viral load=5, Low viral load=14).

Time of treatment	Viral load (IU/ml)			
	Very high	High	Moderate	Low
Pre-treatment	19427000 ± 527847	2374000 ± 331629	914420 ± 31540	258500 ± 20169
After 3months	0 ± 0*	0 ± 0*	0 ± 0*	0 ± 0*

*$p < 0.05$ significant difference between treated and pre-treated values.

Very high; viral load > 10,000,000 IU/ml
High; viral load > 1,000,000 IU/ml
Moderate; viral load > 500,000 IU/ml
Low; viral load < 500,000 IU/ml

Table 2 : Pre-treatment values.

Variables	Group A	Group B	Group C
Hb (g/dl)	14.8 ± 0.4	13.82 ± 0.39	13.1 ± 0.36
WBC (/mm³)	7157.1 ± 583.4	5982.8 ± 403.9	5422.2 ± 325.8
ANC (/mm³)	4198.7 ± 434.2	3370 ± 245.6	3168.7 ± 261.3
PLT (/mm³)	209210 ± 14157	235280± 12978	202060 ± 12483
Plasma glucose level (mg/dl)	103.36 ± 2.5	101.9 ± 1.6	99.17 ± 1.8
ALT (IU/L)	55.1 ± 4.4	59.2 ± 2.86	55.3 ± 3.6
ALP (IU/L)	273.5 ± 13.5	300.5 ± 12.3	353.4 ± 11.2
S.Albumin (g/dl)	4.04 ± 0.1	4.2 ± 0.10	4.01±0.12
Body weight (Kg)	88.07 ± 2.1	66.56 ± 1.83	80.06 ± 3.25

Table 3 : Values three months after starting treatment.

Variables	Group A	Group B	Group C
Hb (g/dl)	13.5 ± 0.3	11.5 ± 0.35	11.5 ± 0.35
WBC (/mm³)	4892.9± 475.9	3800± 305.6	3800± 305.6
ANC (/mm³)	2679.8± 329.9	2015 ± 187	2015.2 ± 187.1
PLT (/mm³)	178930± 10401	158110 ± 12905	158110 ± 12905
Plasma glucose level (mg/dl)	88.57 ± 2.16	90.4 ± 1.5	88.44 ± 2.6
ALT (IU/L)	47.9 ± 3.58	41.3 ± 1.98	45.7 ± 1.9
ALP (IU/L)	192.7 ± 11.6	227 ± 11.09	276.7 ± 9.1
S.Albumin (g/dl)	3.58 ± 0.1	3.8 ± 0.09	3.57±0.096
Body weight (Kg)	80.36 ± 2.4	62 ± 2.39	74.2 ± 3.02

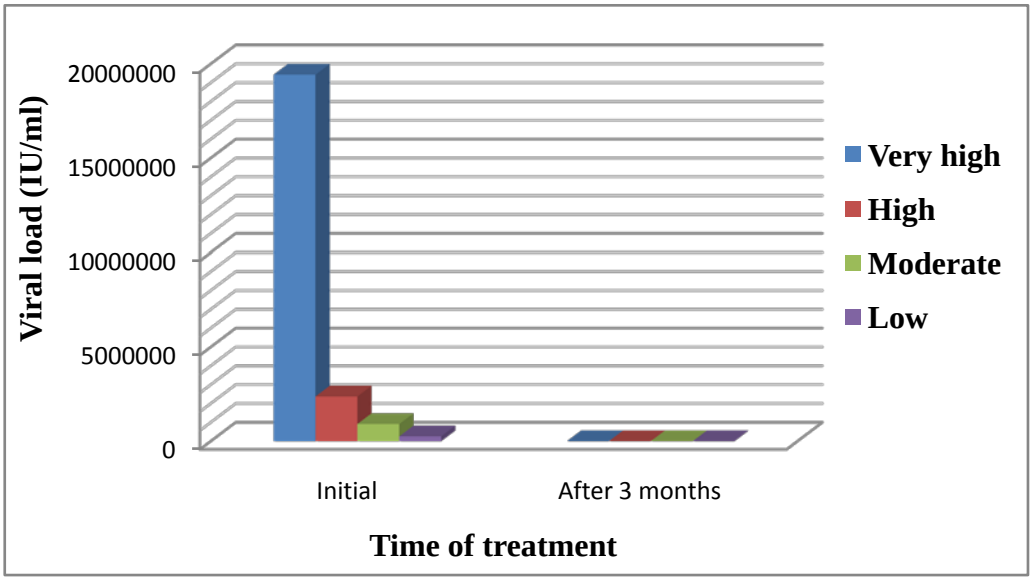
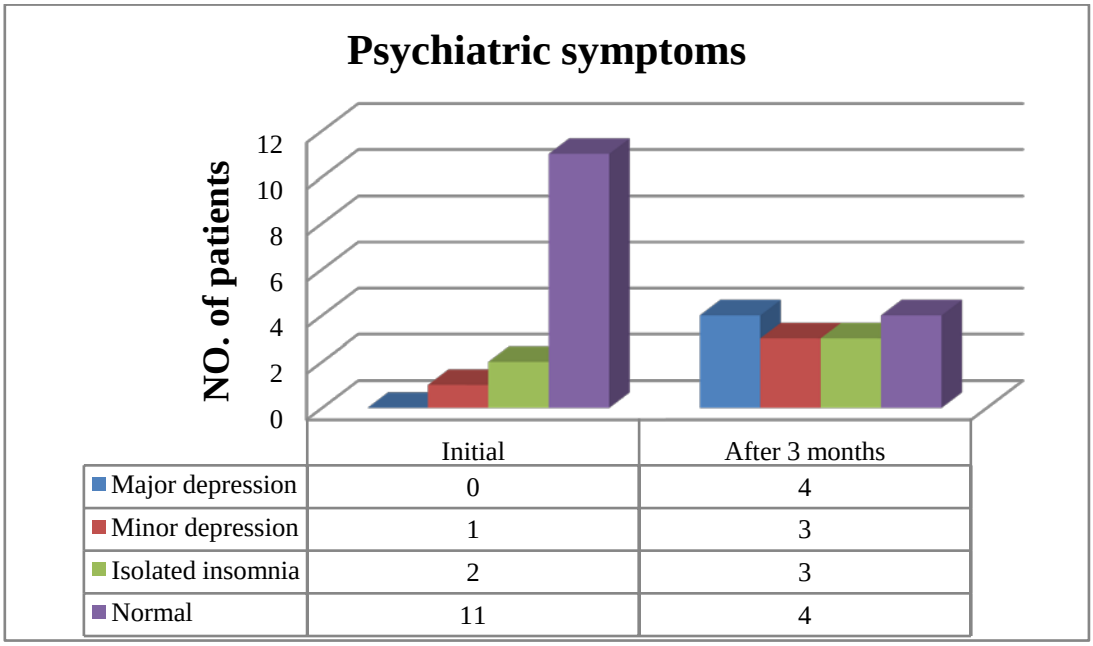


Figure 1 : Histogram showing viral load (amount of virus RNA in serum) in newly diagnosed HCV infected patients, genotypes one and four, treated with s.c. PegIFN α-2a 180 μg/week and RBV 1200, 1000 or 800 mg/day for 3 months (n=47).



	Initial	After 3 months
Major depression	0	4
Minor depression	1	3
Isolated insomnia	2	3
Normal	11	4

Figure 2 : Data chart showing psychological presentation in newly diagnosed HCV infected patients in group A, before treatment and three months after starting treatment with s.c. PegIFN α-2a 180 μg/week and RBV 1200 mg/day (n=14).

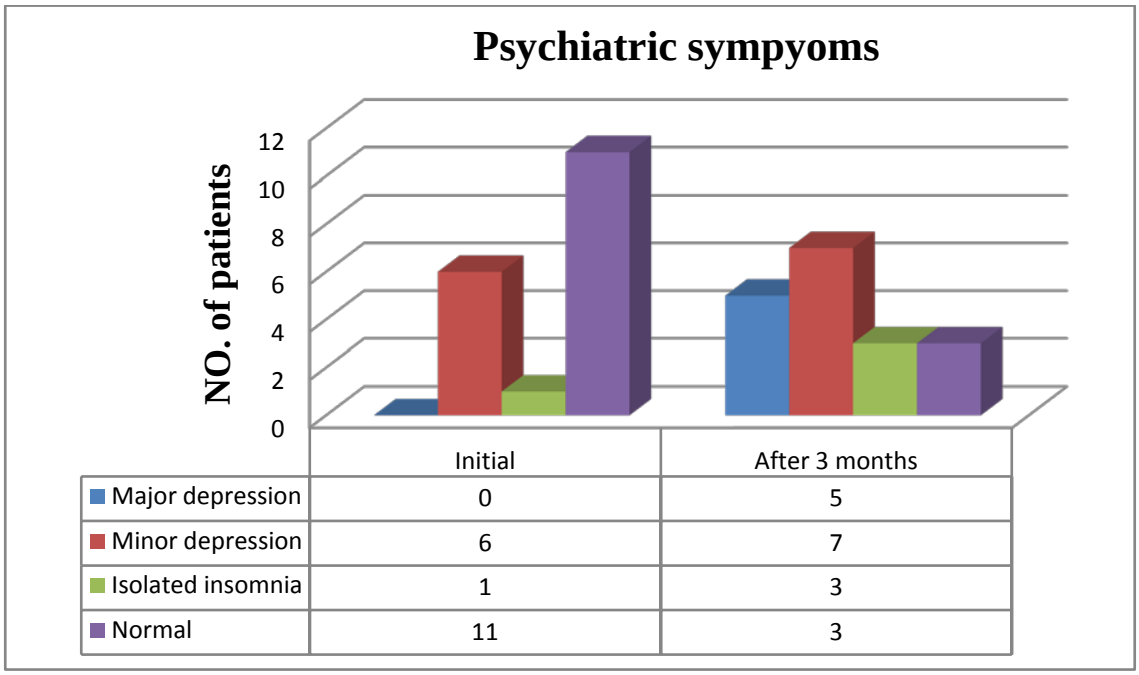


Figure 3 : Data chart showing psychological presentation in newly diagnosed HCV infected patients in group B, before treatment and three months after starting treatment with s.c. PegIFN α-2a 180 μg/week and RBV 1000 mg/day (n=18).

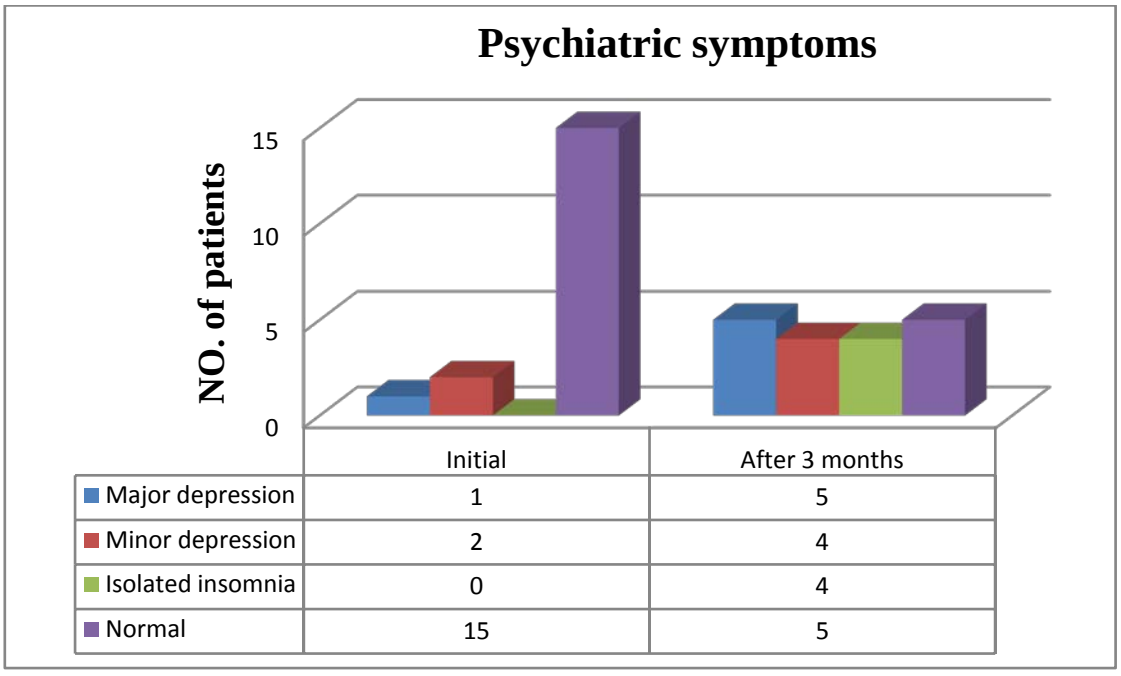


Figure 4 : Data chart showing psychological presentation in newly diagnosed HCV infected patients in group C, before treatment and three months after starting treatment with s.c. PegIFN α-2a 180 μg/week and RBV 800 mg/day (n=18).

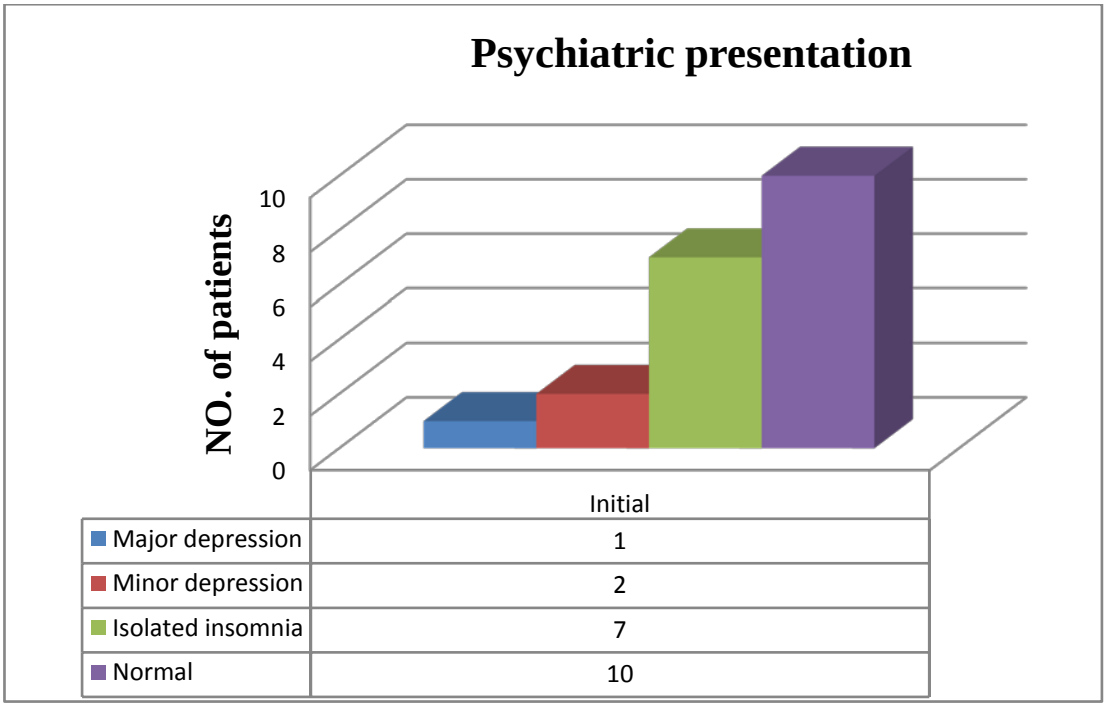


Figure 5 : Data chart showing psychological presentation in control group (n=20).

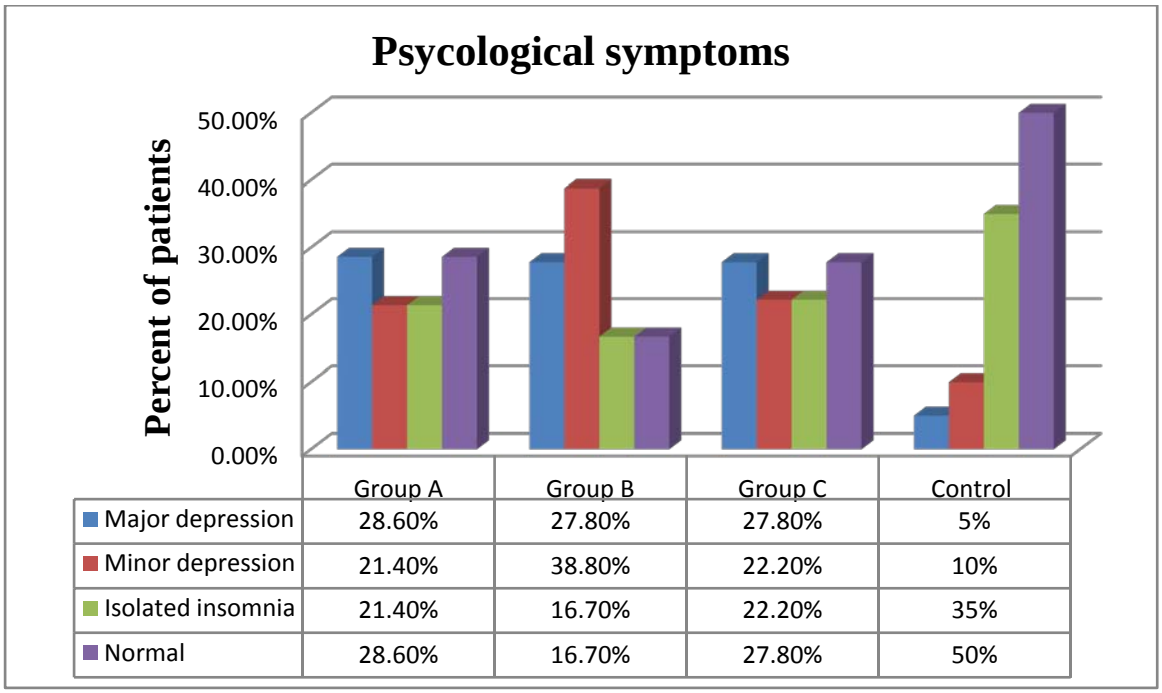


Figure 6 : Data chart showing percent comparison in psychological presentation of A, B, C and control groups (n=70).