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RESEARCH ARTICLE

Naïve Patients withChronic HCVliving in Jazan, Treated with PEG-IFN-α2a and Ribavirin: Rate of Sustained viral response (SVR).

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Manuscript Info *Abstract*

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Background and Aims: Chronic hepatitis C (HCV) infection is one of the major causes of liver cirrhosis and hepatocellular carcinoma worldwide. The aim of this study was to determine the outcome of thesustained virologic response (SVR) rates of Saudipatients with naïve HCV living in Jazan region who received combined treatment.

Materials and Methods:38 adult naïve patients having chronic HCV with high baseline HCV-RNA and liver enzymes were treated with a 48- week course of Pegylated interferon α-2a (PEG-IFN- α2a) and Ribavirin(RBV).HCV-RNA levels were tested at weeks: 12, 24,48 and 72.

Results: Of 38treated patients, only 26 completed a 48- week course of combined treatment consisting of PEG-IFN- α2a and Ribavirin, and thensuccessfully followed up until week 72.Overall early viral response (EVR) was achieved in92.3 % (24/26), while SVR was achieved in 57.7% (15/26)of patients,34.6 % (9/26) failed to achieve SVRand developed relapse, while7.7% (2/26) were considered as non-responders (NR).

Conclusion:combined treatment (PEG-IFN- α2a) and (RBV) is effective in achieving SVR in naïve adults infected with chronic HCV. Young age, Female gender and low viral load were the predictors of SVR in our study.

Introduction

Hepatitis C virus (HCV), a single-stranded RNA virus,belonging to flavi and pestivirus family, was first discovered in the United States (USA) in 1989 as a major causative agent of post- transfusion non-A, non-B patients.[1]HCV is one of the major public health problems and a leading cause of chronic liver disease and hepatocellular carcinoma.[2]At least 6 major HCV genotypes have been identified(genotype 1 up to genotype 6).HCV genotype 4 (HCV-4) is common in Africa and Middle East, in which it is responsible for more than 80% of HCV infections.[3]In Kingdom of Saudi Arabia, HCV-4 was the most prevalent genotype followed by HCV-1 while genotypes 2, 3, 5 and 6 were rarely reported.[4],[5],[6],[7],[8],[9]

Aproximately180 million people are infected worldwide.The main way of transmission of HCV is through blood and blood products. There is high prevalence rate of HCV infection among: HIV patients, patients with Hemophilia, patients on hemodialysis and recurrent blood transfusion.Testing of serum for both antibody to HCV (anti-HCV) and HCV- RNA is needed for the diagnosis of HCV infection. A highly sensitive quantitative HCV- RNA assay is needed for the diagnosis because;also it provides information on the level of virus which is useful in management.[10]

This study was conducted to estimate the rate of SVR among naïve Saudi patients with chronic HCV who received combined treatment.

Materials and Methods

This is a hospital-based study in which we had (retrospectively) analyzed the data of patients who received combined treatment for HCV consisting ofPegylated Interferon α-2a (PEG-IFN α-2a) plus Ribavirin (RBV).All patients were given a once weekly subcutaneous injection regimen of PEG-IFN α-2a (Pegasys; Roche, Basel, Switz, 180 mcg) for 48 weeks and oral Ribavirin (Rebetol; Schering Plough Corp., Kenilworth, N.J., USA) .RBV dosage was determined by body weight 1,000 mg/day (body weight ≤75 kg) or 1,200 mg/day (>75 kg) according to the American association for the study of liver disease (AASLD) guidelines. Our study included those who received treatment in the period between November 2008 to February 2011.The indications for giving anti-HCV treatment were the presence of detectable HCV RNA and elevated serum alanine aminotransferase (ALT) more than 1.5-fold. All the patients were treated in gastroenterology outpatient clinic atKing Fahd central hospital in Jazan region (South west region of Saudia Arabia),before starting treatment a verbal consent was taken from all patients with explanation of benefits and possible risks.Data was obtained from a detailed medical records and analysis was done using SPSS. Inclusion criteria used was adult patients above the age of 18 years with proven chronic HCV infection who received combined treatment. Patients who received PEG-IFN alone (monotherapy) and those with decompensated liver disease were excluded from the study. HCV-RNA was measured using real time Polymerase chain reaction (PCR):(TaqMan HCV ASR; Roche Molecular Systems), with minimal detection rate of 15 iu/ml. HCV-RNA levels were measured at: baseline, 12, 48 and 72 weeks,beside other investigations such as complete blood count (CBC),Liver function tests (LFTs),renal function tests(RFTs) and thyroid function tests(TFTs),serology for hepatitis B and HIV infection and abdominal ultrasonography.

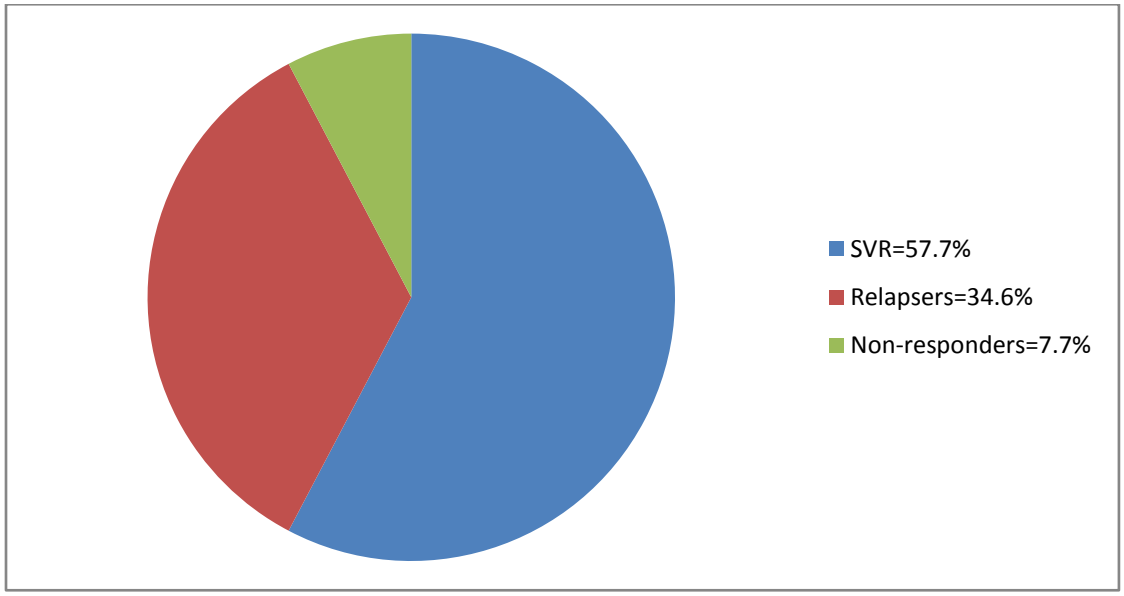
Results

Of 38 naïve patients with chronic HCV whom given combined treatment in the period between Nov.2008 to Feb. 2010, only 26 (68.4%) of them completed a full course of combined treatment (PEG-IFN+RBV) for 48 weeksand were followed up successfully till week 72, whereas 12 (31.6 %) patients failed to comply and they discontinued their treatment by themselves and lost to come for follow up.Of 26 patients who completed their course of treatment(57.7% males,42.3% females), 15/26 (57.7%) of them were successfully achieved sustained viral response (SVR), while 9 (34.6%) patients showed no SVR and developed relapse, but all of them (all relapsers) managed to achieve early viral response and end of treatment response (EVR and ETR).**Table(1),Figure(1).** 2/26(7.7%)of patients failed to achieve EVR at week 12 and so they were considered as non-responders (NR),so their treatment was discontinued by their treating physicians.Overall EVR was achieved in 24/26(92.3%) of patients. The majority of those who achieved SVR were young or middle aged (males,females),11 out of 15 of them(73.3%) their ages were below or equal to 40 years, while 26.7% their ages were more than 40years.Also 10 out 15(66.7%) who achieved SVR their viral load was less than 600,000 iu/l ,while 33.3 had a viral load above 600,000 iu/l. Regarding therelapsers, 6 out of 9(66.7%)had a viral load above 600,000 iu/l, while 33.3% their viral load was below 600,000 iu/l.7 out of 9(77.8%) ofrelapsers were males, while female represent 22.2%.There were no life-threatening side effects during the study and no patients discontinued from the treatment because of a severe adverse event or laboratory abnormality. Because all patients fulfilled the inclusion and exclusion criteria there were no significant co-morbidities.

Table (1): Some characteristics of studied patients

Characteristic	No	%
Gender		
Males	15	57.7%
Females	11	42.3%
Male's age groups		
Age≤40 years	7	26.9%
Age>40 years	8	30.8%
Female's age groups		
Age ≤40 years	6	23.1%
Age>40 years	5	19.2%
Total	26	100%

Figure (1): Outcome oftreated participants



Discussion

The main goal of HCV infection treatment is to prevent complicationssuch as hepatic decompensation,Liver cirrhosis and hepatocellular carcinoma.The recommended drugs for patientswith chronic hepatitis C virus (HCV) infection havebeen the use ofpeginterferon (Peg-IFN) and Ribavirin(RBV). These drugs are given for a duration of48 weeks in case of HCV genotypes 1, 4, 5, and 6 or for 24weeks for HCV genotypes 2 and 3, resulting in sustainedvirologic response (SVR) rates of 40%-50% in patientswith genotype 1 and of 80% or more in patients withgenotypes 2 and 3 infections.[11],[12]

Several forms of virological responses may occur, defined according to their time of occurrence relative to treatment. The most important of which is the sustained viral response (SVR), defined as the clearance of HCV-RNA from serum by a sensitive PCR assay 24 weeks after the end of therapy.SVR is generally considered as a virological cure.[13]

Clearance ofvirus at the end of 24-week or 48-week course of treatment is defined as an end-of treatment response (ETR). An ETR does not accurately predict SVR, but is necessary for it to be achieved.A rapid virological response (RVR), referred to as undetectable HCV RNA at week 4 of treatment,predicts a high likelihood of achieving an SVR.[14] An early virological response (EVR) is defined as a <_2 log reduction or complete clearance of serum HCV RNA at week 12 of therapy compared with pretreatment level. Failure to achieve an EVR is the most sensitive predictor of not achieving SVR.[15] Monitoring viral parameters such as RVR and EVR is so useful for predicting whether or not an SVR islikely to be achieved. In our study all the patients were assessed for EVR,ETR and SVR, but not for RVR.

Patients with HCV genotype 4 infection, combination treatment with pegylated interferon and weight based Ribavirin were given for 48 weeks appears to be the standard regimen, as concluded in a meta-analysis of six randomized clinical trials.[16]

In our study because of no facilities for testing for HCV genotypes during study time, all participants were assumed to have genotype 4,based on the fact that genotype 4 is predominant type in Saudi Arabia (as documented in above literature) and accordingly they was given combined treatment for 48 weeks. SVR in our study was achieved in 58.6% of patients. Similar previousstudies on treatment of HCV genotype 4 (naïve patients) revealed an SVR of 55.5,69%.[17][18],so regarding SVR rate, our results were in consistent with what was documented in the literature.

One large size study conducted in Saudia Arabia by Alashgar*etal* reported an SVR of 55.1%. [9] The small discrepancy between our results and Alashgaretal study results can be explained by that: Alashgar*etal*study included all types of HCV genotypes some patients included in his study had co-morbidities such as HIV infection,Hemophilia,and chronic hepatitis B virus,while all our participants were free from such comorbidities. Another study in treatment of HCV naïve patients with genotype 4 revealed an SVR of 36.7%, but all patients in that study had high viral load(Their baseline viral load was above 800,000 iu/ml).[3]

Some studies have reported two major predictors of an SVR among all studied patients: the viral genotype and baseline viral load.SVR rates were higher in thosewith genotype non-1 infection and in patients with a viral load below 600,000 iu/ml. [12]

Our results are in keeping with this, as it showed that the majority of those who achieved SVR were young or middle (their age below 40 years) with low baseline viral load (Viral load <600,000iu/l and high baselines ALT.While the majority ofrelapsers were males with high viral load.The two non-responders (100%) in our study were males.So age, low viral load and female gender seem to be the predictors of response in our study as well.

Other factors associated with a favorable response include the maximum doses of peg-interferon and Ribavirin, female gender, age less than40 years, non–African American race, lower body weight(<75 kg), those who have no insulin resistance, elevated ALTlevels (three-fold higher than the upper limit of normal), and the absence of bridging fibrosis or cirrhosis on liverbiopsy.[19] [20]

Limitations of current study

It is small size study. Facilities for testing for HCV genotypes were not available in our hospital at timing of the study; also liver biopsy was not done to ensure histological improvement. In the future more large prospective studies are needed to determine prevalence,genotyping, risk factors and other predictors of response for HCV such as RVR in Jazan region.

Conclusion

Ourstudy has shown that combined treatment is effective in achieving SVR in naïvepatients with HCV infection. There is a positive correlation between young age, female gender, low viral load and development of SVR. Proper counseling of patients with HCV patients is mandatory in order to improve treatment adherence.

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References

1.Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. *Science.* Apr 21, 1989, Vol. 244, 4902, pp. 359-62.

2.Williams R. Global challenges in liver disease. HEPATOLOGY 2006;44:521-526.

3.Dimitroulopoulos D, Elefsiniotis, Pavlidi Cs, Xinopoulos D, Tsamakidis K, Patsavela S et al. European *vs*. Egyptian HCV-4 Patients with Elevated Baseline HCV RNA, Treated with PEG-IFN-α2a and Ribavirin: The Role of Rapid and Early Virologic Response. Hepat Mon 2010; 10(3): 193-198.

4.Abdel-Moneim AS, Bamaga MS, Shehab GMG, Abu-Elsaad A-ASA, Farahat FM (2012) HCV Infection among Saudi Population: High Prevalence of Genotype 4 and Increased Viral Clearance Rate. PLoS ONE 7(1): e29781. doi:10.1371/journal.pone.0029781

5.Al-Faleh F, Huraib S, Sbeih F, Al-Karawi M, Al-Rashed R, et al. (1995) Hepatitis C virus genotypes in patients with chronic liver disease and haemodialysis patients from Saudi Arabia. J Viral Hepat 2: 293–296..

6.Osoba AO, Ibrahim M, Abdelaal MA, Al-Mowallad A, Al Shareef B, et al. (2000) Hepatitis C virus genotyping by polymerase chain reaction and DNA enzyme immunoassay among Saudi patients in the Western Province, Saudi Arabia. Ann Saudi Med 20: 394–397.

7.Karkar A (2007) Hepatitis C in dialysis units: the Saudi experience. HemodialInt 11: 354–367.

8.Alzahrani AJ, Obeid OE, Al-Ali A, Imamwardi B (2009) Detection of Hepatitis C virus and Human immunodeficiency virus in expatriates in Saudi Arabia by antigen-antibody combination assays. J Infect Developing Countries 3: 235–238.

9.Al Ashgar H, Khan MQ, Helmy A, Al Swat K, Al ShehriA,AlKalbaniA,et al . Sustained virologic response to peginterferon α-2a and ribavirin in 335 patients with chronic HCV:A tertiary care center experience .Saudi J Gastroenterol 2008;14:58-65

10.Ghany MG, Strader DB, Thomas DL, Seeff LB: Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 2009, 49:1335-1374.

11.Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 2001;358:958-965.

12.Hadziyannis SJ, Sette H Jr, Morgan TR, Balan V, Diago M, Marcellin P, et al.; for PEGASYS International Study Group. Peginterferonalpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Ann Intern Med 2004;140:346-355.

13.Kobayashi S, Takeda T, Enomoto M, Tamori A, Kawada N, Habu D, et al. Development of hepatocellular carcinoma in patients with chronic hepatitisCwho had a sustained virological response to interferon therapy:a multicenter, retrospective cohort study of 1124 patients. Liver Int 2007; 27:186-191.

14.Yu JW, Wang GQ, Sun LJ, Li XG, Li SC. Predictive value of rapid virological response and early virological response on sustained virological response in HCV patients treated with pegylated interferon alpha-2a and ribavirin. J GastroenterolHepatol 2007;22:832-836.

15.Davis GL, Wong JB, McHutchison JG, Manns MP, Harvey J, Albrecht J. Early virologic response to treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C. HEPATOLOGY 2003;38: 645-652.

16.Khuroo MS, Khuroo MS, Dahab ST. Meta-analysis: a randomized trial of peginterferon plus ribavirin for the initial treatment of chronic hepatitis C genotype 4. Aliment PharmacolTher 2004;20:931-938.

17.El-Zayadi AR, Attia M, Barakat EM, Badran HM, Hamdy H, El-Tawil A, *et al* . Response of hepatitis C genotype-4 naive patients to 24 weeks of Peg-interferon-alpha2b/ribavirin or induction-dose interferon-alpha2b/ribavirin/amantadine: A non-randomized controlled study. Am J Gastroenterol 2005;100:2447-52.

18.Kamal SM, El Tawil AA, Nakano T, He Q, Rasenack J, Hakam SA, *et al*. 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;54:858-66.

19.FriedMW,Shiffman ML, Reddy KR, Smith C, Marinos G, GoncalesFL,Jr., et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002; 347:975-982.

20.Romero-Gomez M, Del Mar Viloria M, Andrade RJ, Salmeron J, Diago M, Fernandez-Rodriguez CM, et al. Insulin resistance impairs sustained response rate to peginterferon plus ribavirin in chronic hepatitis C patients.Gastroenterology 2005;128:636-641.