Pegylated vs. Standard Interferon in Combination with Ribavirin for Genotype 2 and 3 in Chronic Hepatitis C: 10 Years Experience in Local Population

Shahid Sarwar,[1] **Anwaar A. Khan,**[2] **Shandana Tarique**[3]

Abstract

Objective: To compare the response in patients of chronic hepatitis C of genotype 2 and 3 to standard interferon (IFN) plus ribavirin vs. Pegylated interferon plus ribavirin.

Type of Study: Cohort type of case series.

Setting: Study was based on 10 years data of patients of hepatitis C treated at Garden Clinic Lahore.

Patients and Methods: Patients of chronic hepatitis C of genotype 2 and 3 were included and treated with either standard IFN plus ribavirin or peg IFN plus ribavirin for 6 months. Response to therapy was evaluated with qualitative PCR for end of treatment response (ETR) and sustained viral response (SVR). Both groups of patients were compared using chi square test.

Results: Total of 609 patients with mean age 39.8 (± 9.37) and male to female ratio 1.67 / 1 (381 / 228) were included. Genotype 3 was seen in 587 (96.4%) patients and genotype 2 in 22 (3.6%). Peg IFN plus ribavirin was given to 51 (8.4%) while 558 (91.6%) patients were treated with standard IFN and ribavirin. Biochemical response was noted in 462 (75.9%) while ETR was seen in 514(84.4%) patients. Relapse was noted in 99 (16.3%) patients, while PCR was negative both at end of treatment and 6 months later in 415 (68.7%) of them. Of patients with positive PCR at end of treatment, 38 had negative PCR 6 months later, while 57 still had positive PCR result. Overall sustained viral response (SVR) was 74.4% (453 / 609). SVR in patients receiving peg IFN was 90.19% (46 / 51) which was significantly better (p value 0.007) than 72.93% (407 / 558), for standard IFN and ribavirin.

Conclusion: Pegylated IFN plus ribavirin had better response in patients of chronic hepatitis C with genotype 2 and 3 as compared to standard IFN plus ribavirin.

Key Words: Chronic hepatitis C, Genotype 2 and 3, Pegylated interferon, Standard interferon, Sustained viral response.

Introduction

Chronic hepatitis C has afflicted more than 170 million person world – over with prevalence in different regions varying from less than 2% in developed countries to 20% in few African countries.[1] Diagnosis of infection is usually late, when patients present with complications i.e. gastrointestinal bleeding, ascites or encephalopathy. Disease is progressive and ultimately fatal at this stage. With increasing awareness and availability of investigations, it is increasingly being diagnosed at early, treatable stage.

Treatment of hepatitis C has evolved from interferon (IFN) monotherapy to combination therapy with

Sarwar S.[1]
Assistant Professor Medicine, King Edward Medical University, Lahore

Khan A.A.[2]
Professor Medicine, Shaikh Zayed Post Graduate Medical Institute, Lahore

Tarique S.[3]
Assistant Professor Medicine, King Edward Medical University, Lahore

addition of ribavirin and from standard interferon to pegylated interferon (Peg IFN). It has not only led to improved outcome but has also resulted in convenience of weekly therapy.[2] Sustained viral response (SVR), i.e. undetectable virus with polymerase chain reaction (PCR) six months after completion of therapy, which is used for defining response to treatment, has improved from < 40% with IFN monotherapy to > 80% with pegylated IFN along with ribavirin especially in genotype 2 and 3.[3]

Cost of interferon therapy is still a major hurdle in its widespread use in the developing countries. According to one study, 15.4% patients of hepatitis C do not opt for treatment due to non-affordability.[4] Newer forms of treatment have further added to the cost of therapy. Use of Peg INF instead of standard IFN results in five fold increase in treatment expenditure so that standard interferon is still the predominant form of therapy in Pakistan despite widely reported better outcome with Peg IFN based combination therapy.[5]

Few studies have identified genotype 3, to be the predominant type of virus in our population.[6] Difference in response to Peg IFN and standard IFN in combination therapy for genotype 3 is much less than is seen in genotype 1, 4, 5 or 6. There are studies with no significant difference in outcome of therapy among two forms of treatment,[7] whereas better response with peg IFN plus ribavirin, is also being reported by others for genotype 3.[8] It will be pertinent to compare the difference in outcome of therapy in our patients for standard IFN vs. Peg IFN based combination therapy. It will also answer a frequently asked question; are we compromising on possibility of achieving better sustained viral response by opting for standard IFN instead of peg IFN in our population due to financial constrains?

Objective of our study was to compare the response to standard interferon and Pegylated interferon based combination therapies in patients of chronic hepatitis C with genotype 2 and 3.

Patients and Methods

It was a case series of cohort pattern which was based on computerized database of patients with chronic hepatitis C treated at the Garden clinic over last 10 years. Patients with genotype 2 and 3 who received interferon therapy for 6 months and in whom outcome measures like end of treatment response (ETR) and sustained viral response (SVR) had been recorded, were included in final analysis. Patients with genotype other than 2 and 3, those treated for less than 6 months or beyond 6 months and those lost to follow up with no record of ETR and SVR were excluded. Patients with positive hepatitis B surface antigen, positive HIV, other chronic liver diseases i.e. alcoholic liver disease, hepatotoxic drugs, autoimmune chronic hepatitis, haemochromatosis, wilson's disease and cirrhosis with child class C were also excluded. Decision to treat patient with standard IFN or Peg IFN therapy was non-randomized, based on affordability of patient and availability (Peg IFN was only available after 2001).

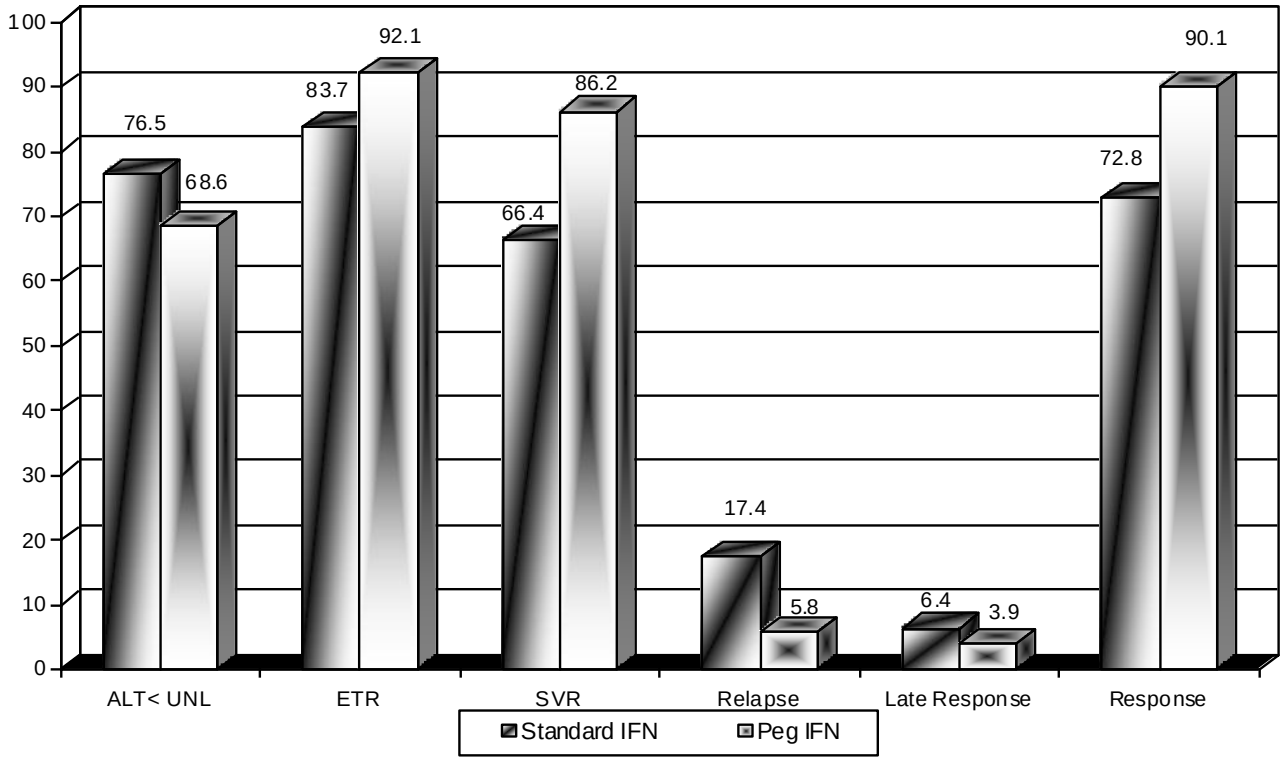
Variables of patients at the outset including age, sex, weight, bilirubin, baseline alanine aminotransferase (ALT), Hemoglobin, Platelet count, were noted. Patients who received 80% of standard dose and duration of therapy were declared to have completed treatment. Standard therapy was defined as 72, thrice weekly injections of standard interferon or 24, weekly injections of Pegylated interferon along with ribavirin $\geq$ 800 mg / day. End of treatment response (ETR) and sustained viral response (SVR) were determined for each patient with qualitative PCR having lower limit of detection as 50 IU/ml. PCR was carried out by Nested PCR, based on five major processes, i.e. extraction of HCV RNA from serum sample, reverse transcription of target RNA to generate c DNA, two rounds of PCR amplification and detection. ETR was defined as negative qualitative PCR at end of treatment while SVR was defined as negative PCR six months after completion of therapy. Patients with PCR positive, at end of treatment and also six months after treatment completion, were declared as non-responders, whereas, those with positive PCR at end of treatment and negative PCR, six months after completion of therapy were defined as late responders. Relapse was defined as negative end of treatment PCR but positive PCR after six months of completion of treatment. Definitions used were as per AASLD guidelines.[2]

Statistical Analysis

Results were analyzed using software package (SPSS 12.0.; SPSS Inc, 1989 – 1999 Chicago, Ill). Results were expressed as mean ± SD. Categorical variables were expressed in percentage. Patients treated with standard IFN and ribavirin were compared with those treated with Peg IFN and ribavirin using student's t test for numerical variables and chi square test and cross tabulation for categorical variables. Results were

Table 1: Comparison of patients on Peg IFN therapy and standard IFN.

Variables	Peg IFN and ribavirin therapy	Standard IFN and ribavirin therapy	P value
Age (Years)	40.05 (± 9.00)	39.78 (9.4)	0.84
Male / Female	32 / 19	349 / 208	0.95
Mean ALT (IU/ml) (At treatment start)	133.35 (62.05)	118.22 (97.20)	0.27
Mean Weight (Kg)	73.93 (13.40)	68.36 (12.50)	0.009
Mean Hb (g/dl)	13.74 (1.49)	13.40 (1.77)	0.19
Genotype 3 / 2	51 / 0	536 / 22	0.14



Graph 1: Comparison of response to therapy with peg IFN plus ribavirin vs standard IFN plus ribavirin.

analyzed as per protocol and only patients with PCR test for HCV RNA at end of treatment and six months later were included in final outcome analysis. P value of < 0.05 was considered significant.

Results

Total of 817 patients were treated at Garden Clinic over 10 years for chronic hepatitis C with interferon and ribavirin therapy. Genotype 2 and 3 was diagnosed in 721 patients, out of which 609 patients, who completed therapy as per protocol were included in final analysis. Treatment had to be stopped earlier due to side effects in 32 (4.7%) patients, 44 continued treatment for 6 – 9 months, 30 patients for 9 – 12 months, whereas 6 received treatment for more than one year, and all these were excluded.

Mean age of patients included was 39.8 (± 9.37) and male to female ratio was 1.67 / 1 (381 / 228). Mean weight of study patients was 69.04 (± 12.7) while mean ALT at start of treatment was 119.49 U/L (± 94.82). Type 3 was the predominant genotype, noted in 587 (96.4%) patients whereas 22 (3.6%) patients

were of genotype 2. Pegylated interferon in combination with ribavirin was given to 51 (8.4%) and 558 (91.6%) patients were treated with standard interferon and ribavirin. Table 1 shows the comparison of patients on Peg IFN based therapy and those treated with Standard IFN therapy. Significantly more obese patients were in peg IFN based combination therapy cohort.

Biochemical response with serum ALT < upper normal limits (UNL), was noted in 462 (75.9%) patients, while virological response, ETR was seen in 514 (84.4%). Relapse was noted 6 months after completion of treatment in 99 (16.3%) patients, while PCR was negative both at end of treatment and 6 months later in 415 (68.7%). Of patients with positive PCR at end of treatment, 38 had negative results 6 months later (late responders), whereas 57 still had positive PCR. Overall sustained viral response (SVR) in study patients was 74.4% (453 / 609).

SVR in patients receiving peg IFN was 90.19% (46 / 51) whereas it was 72.93% (407 / 558) in patients treated with standard IFN and ribavirin. Significantly better response was seen with Peg IFN based combination therapy (p value 0.007), although the number of study patients was vastly different, the peg IFN patients were large enough for comparison.

Discussion

Response with Pegylated interferon plus ribavirin is our study is around 90%, better than the one, seen with standard interferon. Superiority of peg IFN in patients of genotype 1 is well proven and it is the only treatment option recommended due to poor response with standard interferon.[2] But response with non-Pegylated IFN in genotype 2 and 3 is better and is still the predominant form of therapy used due to its lower cost. At the same time Pegylated IFN has maintained its edge over standard IFN even in genotype 2 and 3 as far as SVR is concerned. Shephard J et al reported that peg IFN reduces the risk of remaining infected with HCV by 17% when compared with standard interferon. They found peg IFN well tolerated with no difference in side effect profile.[9] Response in excess of 80% was noted in another study by Hadziyannis SJ et al in genotype 2 and 3.[10] Studies from South Asian region with head to head comparison of standard IFN versus Peg IFN along with ribavirin are scanty. Small case series have shown superiority of Peg IFN in treating non-responders to standard interferon based combination therapy in our population.[11,12]

Contrary to what is concluded in above mentioned studies, Lee SD et al from Taiwan found no statistically significant difference in response to two forms of therapies despite reporting SVR as 68.4% and 86.8% for standard IFN and peg IFN respectively. Number of dropouts and adverse events were also more in patients treated with peg IFN plus ribavirin.[7]

Despite much improved response with Pegylated IFN based therapy as noted in our study, fact remains that cost of treatment is many times more, when compared with non-Pegylated form of therapy, but cost effectiveness of a treatment is determined by taking into account multiple factors like average life expectancy, quality adjusted life expectancy, life time cost of health care and likelihood of disease progression as recommended by Markov Model.[13] Sullivan SD et al concluded that peg IFN plus ribavirin is cost effective as compared with standard IFN when above mentioned factors are taken in to account.[14] Siebert U et al found that peg IFN along with ribavirin reduces the incidence of liver complications, prolongs life and improves the quality of life.[15] Treatment of patients with persistently normal alanine aminotransferase (ALT) with standard interferon was not recommended in the past, but peg IFN plus ribavirin reduces 30 years risk of cirrhosis by 9% in those with normal ALT and is found to be cost – effective.[16]

Our study is first of its nature with direct comparison of two forms of interferon therapies available, from this region. It spans over 10 years with large sample size. Distribution of patients in two groups, Pegylated vs. non-Pegylated IFN, was non-randomized and number of patients in two cohorts were disproportionate as treatment choice was determined largely by economic status of patients. Significant number of patients had to be excluded from final analysis either due to premature termination of treatment or continuation of therapy beyond 6 months to avoid confounding of results. These limitations of study are due to real life setting, instead of being a controlled therapeutic trial. It will be pertinent to mention that standard interferon plus ribavirin has also shown good results and will continue to be the dominant form of therapy for hepatitis C, due to poor socioeconomic status of majority of our patients. Proper counseling of patients regarding pros and cons of both types of injections is needed and it appears that peg IFN based combination therapy is cost – effective in view of long term consequences of disease itself.

Conclusion

Pegylated IFN plus ribavirin had better response in patients of chronic hepatitis C with genotype 2 and 3 as compared with standard IFN plus ribavirin.

Reference

1. Global surveillance and control of hepatitis C. Report of WHO consultation organized in collaboration with the viral hepatitis Prevention Board. Antwerp Belgium. J Viral Hepat 1999; 6: 35-47.
2. Fried MW, Shiffman ML, Reddy KR, Smith C, Mavinos G, Goncales FL Jr et al. Pegylated interferon alpha 2a plus ribavirin for chronic hepatitis C virus infection. N Eng J. Med 2002; 347 (13): 975-82.
3. Dienstag JL, McHutchison JG. American Gastroenterology Association medical position statement on the management of hepatitis C. Gastroenterology 2006: 130.
4. Sood A, Midha V, Sood N, Bansal M. Antiviral treatment for chronic hepatitis C: Reasons for non-treatment in a northern Indian center. Ind. J. Gastroenterol 2006; 25 (6): 319-20.
5. Hamid S, Umar M, Alam A, Siddiqui A, Qureshi H, Butt J. PSG consensus statement on management of hepatitis C virus infection – 2003. J Pak Med Assoc 2004; 54 (3): 146-50.
6. Sarwar S, Butt AK, Khan AA, Alam A, Ahmad A, Dilshad A. Serum alanine aminotransferase levels and response to interferon – ribavrin therapy in chronic hepatitis C patients. J Coll Physicians Surg 2006; 16 (7): 460-3.
7. Lee SD, Yu ML, Cheng PN, Lai MY, Chao YC. Comparison of a six month course pegylated interferon alpha 2b plus ribavirin and interferon alpha 2b plus ribavirin in treating Chinese patients with chronic hepatitis C in Taiwan. J Viral Hepatol 2005; 12 (3): 283-91.
8. Strader DB, Wright T, Thomas DL, Seeff LB. Diagnosis, management and treatment of hepatitis C. Hepatology 2004; 39: 1147-71.
9. Shephard J, Brodin H, Cave C, Waugh N, Price A, Gabbay J. Pegylated interferon alpha 2a and 2b in combination with ribavirin in the treatment of chronic hepatitis C: a systematic review and economic evaluation. Health. Technol. Assess 2004; 8 (39): 1-125.
10. Hadziyannis SJ, Sette H. Jr, Morgan TR et al. Peginterferon alpha 2a and ribavirin combination therapy in chronic hepatitis C: A randomized study of treatment duration and ribavirin dose. Ann. Inter. Med 2004; 140: 346-55.
11. Ahmad SI, Mahmud MR, Khan NY, Naseemullah M, Hanif M. Pegylated interferon and ribavirin in HCV genotype 3 detectable patients after 12 weeks of conventional interferon – ribavirin treatment. Pak J. Gastroenterol 2006; 20 (1): 58-62.
12. Muhammad N, Jan A, Rehman N. Outcome of combined Interferon – Ribavirin in the treatment of chronic Hepatitis C. J Coll Physicians Surg Pak Nov 2004; 14 (11): 651-3.
13. Benett WG, Inoue Y, Beck JR et al. Estimates of the cost effectiveness of a single course of interferon alpha 2b in patients with histologically mild chronic hepatitis C. Ann. Intern Med 1997; 127: 855-65.
14. Sullivan SD, Craxi A, Alberti A, Giuliani G, De Carli C, Wintfeld N et al. Cost effectiveness of peg interferon alpha 2a plus ribavirin versus interferon alpha 2b plus ribavirin as initial therapy for treatment naïve chronic hepatitis C. Pharmacoeconomics 2004; 22 (4): 257-65.
15. Siebert U, Sroczynoski G, Ross S, Wasem J, Raven-Sieberer U, Kurth BM et al. Cost effectiveness of pegylated interferon alpha 2b plus ribavirin versus interferon alpha 2b plus ribavirin for initial treatment of chronic hepatitis C. Gut 2003; 52 (3): 425-32.
16. Hornberger J, Farci P, Prati D, Zeuzem S, Green J, Patel KK. The economics of treating chronic hepatitis C patients with pegylated interferon alpha 2a plus ribavirin, presenting with persistently normal ALT. J Viral Hepatol 2006; 13 (6): 377-86.