ORIGINAL ARTICLE

PREDICTIVE VALUE OF EARLY VIRIOLOGICAL RESPONSE FOR SUSTAINED VIRIOLOGICAL RESPONSE IN CHRONIC HEPATITIS C WITH CONVENTIONAL INTERFERON THERAPY

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Background: Hepatitis is a major public health problem in Pakistan due to its strong association with liver failure and hepatocellular carcinoma. In Pakistan, conventional interferon therapy along with Ribavirin is favoured especially in Government funded programs for treatment of Hepatitis C, over the more expensive Pegylated Interferon and Ribavirin combination therapy as recommended by Pakistan society of Gastroenterology and GI endoscopy due to its favourable results observed in genotype 3 which is the dominant genotype of this region. Objective of our study was to assess the viriological responses with standard interferon therapy and to determine the predictive values of early viriological response (EVR) for Sustained Viriological Response (SVR) in chronic hepatitis C patients treated with standard interferon therapy. M**ethods**: A cross sectional study was conducted on patients with chronic hepatitis C having received standard interferon and ribavirin therapy for six months. EVR and SVR were noted for analysis. Positive and negative predictive values of EVR on SVR were calculated. **Results:** Out of the total sample (N=3075), 1946(63.3%) patients were tested for EVR. 1386 (71.2%) were positive while 560(28.8%) were negative while 516 (16.8%) were tested for SVR. Two hundred and eighty-five (55.2%) were positive while 231 (44.8%) were negative. EVR and SVR tested were n=117. Positive predictive value of EVR on SVR was 67.1% and negative predictive value was 65.8%. Statistically significant association between EVR and SVR was determined with Chi square statistic of 11.8 (p-value <0.0001). **Conclusion:** EVR is a good predictor of response of patients to standard interferon and ribavirin therapy. In the absence of an EVR, it seems imperative to stop further treatment. Virilogical responses with conventional interferon therapy are comparable to those of pegylated interferon therapy so adoption of conventional INF therapy is justified in terms of its cost effectiveness especially in resource constrained nations like Pakistan.

Keywords: Interferon, hepatitis C, predictive value of tests

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INTRODUCTION

Hepatitis C virus (HCV) is the major cause of liver disease in industrialized as well as developing countries. Hepatitis is a major public health problem due to its strong association with liver failure or hepatocellular carcinoma, both very fatal conditions. WHO has estimated that about 180 million people in the world are infected with HCV. Out of these 130 million people are chronic HCV carriers and are at great risk of developing liver cirrhosis and cancer.[1] About 3% of the world population has hepatitis C infection. According to another estimate, 350 000 to 500 000 people die each year from hepatitis C-related liver diseases. Although INF treatment has achieved great popularity in recent years, this treatment is known to be successful in 50–90% of persons treated contributing towards overall lowering of liver cancer and cirrhosis.[2]

According to statistics, in different regions of Pakistan prevalence of Hepatitis C is about 2.2–13.5%. This wide range of prevalence is due to inadequate record keeping and lack of diagnostic facilities in outreach areas. In Pakistan, conventional IFN therapy along with Ribavirin is favoured especially in Government funded programs for treatment of Hepatitis C, over the more expensive Pegylated Interferon and Ribavirin combination therapy as recommended by Pakistan society of Gastroenterology and GI endoscopy due to its favourable results observed in genotype 3 which happens to be the dominant genotype of this region.[3] Relapse rate has also markedly decreased as compared to the past with the success of Interferon and Ribavirin combination therapy.[4] However much work remains to be done to optimize treatment for chronic hepatitis C. Many factors govern the success of INF treatment in patients one of which is patient adherence with the therapy.[5]

Predictors of response to interferon therapy may ultimately help physicians in identifying patients who have the least probability of achieving an SVR. Thus exorbient costs can be averted timely by

aborting treatment midway and thus perhaps sparing the patients the side effects and cost of therapy. Significant advances have been made in the treatment of HCV with reported SVR rates rising to greater than 50% with the use of pegylated interferon and ribavirin combination therapies.[6] Despite encouraging results shown by pegylated Interferon therapy current data are more in favour of IFN than PEG-IFN if efficacy and safety are the only factors under consideration.[1]

As interferon therapy is not successful in 100 per cent of patients, on treatment virilogical responses can be used to screen out patients who would not ultimately respond to therapy thus reducing the financial costs of nationwide hepatitis programs. Also financial burden on a resource constrained nation like Pakistan can be reduced by eliminating unnecessary expensive tests from treatment protocol. This study intends to highlight the usefulness of EVR as a predictor of outcome of treatment therapy in the form of negative SVR. The study was done with the objectives to assess the viriological responses with standard interferon therapy and too determine the predictive values of EVR for SVR in chronic hepatitis C patients treated with standard interferon therapy

MATERIAL AND METHODS

A cross-sectional study was conducted on patients with chronic hepatitis C (n=3075) enrolled in Hepatitis Control program from Jan 2009 till Dec 2013 in Holy Family Hospital, Rawalpindi. All patients included had received conventional interferon therapy comprising of standard interferon (INF) 3 MIU, subcutaneously, three times a week plus Ribavirin 800–1200 mg in divided doses daily for a period of six months.

Patient files were reviewed and required variables were selected for analysis. Documented early viriological responses (EVR) which was HCV RNA qualitative PCR after 12 weeks of therapy with conventional interferon and Sustained Virilogical responses (SVR) which was HCV RNA qualitative PCR after 24 weeks of completion of conventional interferon therapy were noted for analysis. Positive and negative predictive values of EVR on SVR were calculated for n=117 patients. All studied patients were HCV RNA positive by PCR with raised ALT levels at the beginning of treatment. None of the patients were cirrhotic as determined clinically and by ultrasound. None of the patients were co infected with HBV. Analysis was done using SPSS version 21. Positive and negative predictive values were calculated. Chi square test was applied wherever applicable. *p*-value less than 0 .05 was considered significant.

RESULTS

Total numbers of patients in the study were 3075. Mean age of the patients was 35.5 with range 15–62. Female patients were 1594 (52%). Male patients were 1473 (48%). 2565 (85%) were married while 440 (15%) were unmarried.

Out of the total sample 1946 (63.3%) patients were tested for early viriological response (EVR). Thirteen hundred and eighty-six (71.2%) were positive while 560 (28.8%) were negative while 516 (16.8%) were tested for Sustained viriological response. Two hundred and eighty-five (55.2%) were positive while 231 (44.8%) were negative.

In our sample patients with both EVR and SVR tested were N=117. Positive predictive value of EVR on SVR was 67.1% and negative predictive value was 65.8%. Statistically significant association between EVR and SVR was determined with Chi square statistic of 11.8 (*p*-value <0.0001).

Table-1: Relationship between early viral responses with Sustained viral response

Early viriological response (n=117)	Sustained viral response				x^2 (*p*-value)
	Achieved	Achieved	Not achieved	Total	
		51	25	76	11.8 (<0.0001)
	Not achieved	14	27	41	

DISCUSSION

The combination of interferon and ribavirin is safe and effective for the treatment of naive patients with chronic hepatitis C. We attempted to see the effectiveness of standard interferon therapy in terms of virilogical responses in our study. 71.2% patients achieved an EVR with the combination of interferon and ribavirin. This response is somewhat higher than the one Napoli *et al* noted in their study which was 56.2%.[7] However, our EVR response is comparable to the EVR achieved by pegylated interferon therapy as concluded by Davis et al who evaluated data from an international trial reported by Manns *et al* which revealed 60.3% patients losing detectable HCV RNA after 12 weeks of therapy with pegylated interferon therapy.[8] In a meta-analysis conducted in Ottawa on pegylated interferon therapy, results indicated that 70% of subjects (95% CI 58%–81%) achieved EVR.[9]

In our study 55.2% patients achieved an SVR. This response was somewhat lower than those seen in some other studies conducted in Pakistan. Farooqi *et al* in their study conducted at Khyber Teaching Hospital, Peshawar noted 81.39% males and 86.36% female responded to conventional interferon therapy in terms of positive SVR[10] while Jadoon *et al* in their study concluded SVR after 6 months of treatment was 86.4% (*p*=0.034).[11] According to a meta-analysis conducted in England,

SVR after standard interferon combination therapy was 33% (95% CI 29–37) in treatment naïve patients.[12] Comparing these responses with that obtained by pegylated interferon therapy by other studies we noted comparable figures to the ones in our study as depicted by Lucasiewicz *et al*, who obtained 60% SVR in their patients.[13] While meta-analysis on pegylated interferon therapy revealed an SVR amounting to 58% (95% CI, 53–64%).[9]

We noted a highly significant association between EVR on SVR corresponding to results of other studies where EVR has been considered a robust predictor of SVR. Very few patients without an early virological response (EVR), achieve an SVR as was seen by the positive and negative predictive values of the fore mentioned in our study. The same notion has been emphasized by Chen SH in his article where according to him with interferon alpha therapy in patients who achieve an EVR, the likelihood of an SVR is 72% and as negative predictor, non-EVR is even and more robust predictor, as in cases without an EVR, the likelihood of an SVR is approximately 0% to 2%.[14] Napoli et al found the positive predictive value of Pegylated INF therapy to be 80%.[7] David GL collected data from 2 large clinical trials of peginterferon and ribavirin and found the negative predictive value of EVR in pegylated INF therapy to be as high as 98.4% while positive predictive value was 68%.[15] Thus a negative EVR has proved highly valuable in making a decision to stop therapy in those patients considered highly unlikely to achieve SVR.

Our findings relating to viriological responses from standard INF therapy are comparable to that of published data on pegylated INF therapy which reinforces the practice of adopting standard Interferon regimen in resource constrained set ups but our findings need to be interpreted in the light of certain inherent limitations like not having data comparing side effects of the two treatments as well as prevalence of genotype 3a in Pakistan, a genotype favouring response rates standard INF treatment.

We recommend EVR should be routinely measured in INF therapy and stopping of treatment in case of negative EVR saves treatment costs and prevents patients from side effects of interferon therapy. Also this treatment requires a moderately complex regimen that includes frequent subcutaneous injections and oral administrations of ribavirin, and frequent monitoring of adverse effects and laboratory results. Unfortunately, adherence to therapy can be poor, which may cause a reduction in treatment response.[16] Adherence is an important factor for the success of the treatment.[17] In our study the size of our cohort was significantly reduced while calculating SVR due to non-adherence to treatment and incomplete reporting of laboratory results (viriological responses). Determining of viriological responses is an expensive business and most of the time in our set up patients have to fund these tests out of their own pockets so non-compliance and attrition problems have frequently been reported which a limitation was observed in our study as well.

CONCLUSION

In conclusion EVR is a good predictor of response of patients to standard interferon and ribavirin therapy. In the absence of an EVR, it seems imperative to stop further treatment. Virilogical responses with conventional interferon therapy are comparable to those of pegylated interferon therapy so adoption of conventional INF therapy is justified in terms of its cost effectiveness especially in resource constrained nations like Pakistan.

AUTHOR'S CONTRIBUTION

AA: Conducted the study, data analysis, manuscript writing. MU, HBK: Supervised the study, proof reading. AK: Data analysis, literature review. ZM, SA, NH, WM: Data collection and organization. FH: Proof reading

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