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Conventional Interferon Therapy Response among Chronic HCV Patients in Khyber Pakhtunkhwa

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Abstract

As Hepatitis C infection is the cause of hundreds of thousands of deaths worldwide including Pakistan. Different regions have different infection rates in Pakistan and hence different mortality. Khyber Pakhtunkhwa (KPK) is one of the main affected provinces of the country. Since Interferon (IFN) based therapy is used to eradicate the infection from the bodies of infected individuals. However information regarding treatment response in different population groups in case of chronic HCV patients is lacking. So it is aimed to investigate response rates of IFN and Ribavirin combination therapy in different districts of KPK.

A total of 198 anti-HCV and PCR positive patients were selected from district Swabi, 54 from Kohat and 89 from Bunir for conventional IFN therapy keeping in mind therapy exclusive criteria for patients. All the patients were given 3MIU thrice a week and 300-400 mg thrice a day, dose of conventional IFN and Ribavirin respectively. Therapy was continued for six months with repeated investigations of CBCs and LFTs during and at the end of course. PCR test was also repeated during (3 months) and at the end of treatment (6 months).

Out of total 341, selected patients for standard IFN- based therapy, 288 (81%) showed ETR while 53 (19%) did not show response. In different districts of KPK, the ETR rates were, 92% in district Swabi, 71% in Bunir and 80% in district Kohat. All these patients having positive ETR were negative for HCV RNA at the end of six months of conventional IFN therapy.

IFN therapy response varies among different population groups of KPK but the average response rate is good enough against HCV infection. This high response may be attributed to responsive genotypes prevalent in KPK.

Keywords: IFN (Interferon); PCR (Polymerase chain reaction); KPK (KhyberPakhtunKhwa); CBCs (Complete blood counts); LFTs (Liver function tests); ICT (Immunochromatographic technique)

Introduction

Hepatitis C is the liver inflammation caused by hepatitis C Virus (HCV), identified in 1989 [1]. HCV genome is 9600 nucleotide long encoding for ten different proteins [2]. HCV infection leads to severe liver diseases like cirrhosis and hepatocellular carcinoma and is the leading cause of death worldwide. About 3% of the world population has hepatitis C infection [3]. In different regions of Pakistan its prevalence is about 2.2 to 13.5% [4-6].

To eradicate hepatitis C infection, Food and Drug Agency (FDA) and National Institute of Health (NIH) has recommended the use of IFN [7]. In Pakistan two types of IFN are used to treat hepatitis C patients, conventional IFN with Ribavirin in combination and Pegasys (peg) with Ribavirin in combination, depending upon the genotype and socioeconomic status of the patients. But mostly conventional IFN are used to treat HCV infection as Pakistan society of Gastroenterology and GI endoscopy has also given the recommendation of using conventional IFN therapy especially in genotype 3 [8]. As treatment response varies among the individuals depending on the genotype [9]. In Pakistan the most responsive genotypes 2 and 3 are prevalent [10], that is why conventional IFN are mostly used.

Many studies have been done to find out response of IFN based therapy in Pakistan. In KPK, some studies have also been done to find out response of conventional IFN therapy [11-13]. All these studies are done randomly, not indicating a particular region and cast. Since response maters the cast and genotype prevalent in that particular region [14] that is why need exist to know about the response of conventional IFN combination therapy in particular regions among chronic HCV patients in KPK.

Methodology

In order to determine End of Treatment Response (ETR), we selected patients from district Swabi, district Bunir and district Kohat. In these districts, we randomly selected patients of different age and sex from different villages. A total of 198 patients were selected from district Swabi, 54 from Kohat and 89 from Bunir for standard IFN and Ribavirin combination therapy (Table 1).

All the patients were subjected to screening (ICT and ELISA) process, followed by confirmation of active HCV infection by PCR. Before starting therapy, all the essential tests including CBCs, LFTs,

Regions	Total no. of samples	Age groups	M/F	ETR+	%ETR+	NR	%NR
Swabi	198	16-45	97/101	182	92	16	8
Bunir	89	18-60	51/38	63	71	26	29
Kohat	54	17-52	28/26	43	80	11	20
Total	341		176/65	288	81	53	19

ETR (End of Treatment Response), NR (Non Responder), M/F (Male/Female)

Table 1: End of treatment virologic response (ETR) in different regions of KPK.

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ultrasound and the exclusion criteria that is previous history of non response, cirrhosis, co-infection and age more than 60 etc was duly considered. The inclusion criteria were age less than 60 years, normal CBCs, non alcoholic patients and initial therapy. The patients fulfilling inclusion criteria were selected for IFN therapy. All the patients were given 3MIU dose of standard IFN thrice a week and Ribavirin with a dose of 300-400 mg thrice a day depending on the weight of the person. This therapy combination was continued for six months with repeated investigations of CBCs and LFTs during and at the end of course. Special instructions were given to patients to come and test their LFTs and CBC at particular times. PCR test was also repeated during (3 months) and at the end of treatment (six months).

After completion of six months therapy and confirmation of IFN response by PCR, the responders and non responders were separated. All the non responders from Swabi district were again treated with the same IFN but with the different dose and duration. This time the dose of IFN was 6MIU but the duration was two months. Again at the end of two months, PCR test was repeated followed by analysis of all the enrolled patients.

Results

Anti-HCV and PCR positive patients were selected for IFN and Ribavirin combination therapy keeping in mind IFN therapy related contraindications. Before starting therapy, thirty three patients were dropped because of the contraindications. The remaining (341) patients completed six months combination therapy. The adverse effects noted during and after the therapy are given in table 2.

Out of total 341 selected patients for standard IFN- based therapy, 288 (81%) showed ETR and were negative for HCV RNA while 53 (19%) did not show response to IFN therapy and were positive for HCV RNA. In district Swabi, 182 (92%) patients were negative and 16 (8%) were positive for HCV RNA at the end of six months treatment. In Bunir, 63 (71%) showed ETR and 26 (29%) did not show response to IFN therapy. In district Kohat, out of 54 patients, 43 (80%) were negative for HCV RNA and only 11 (20%) were positive for HCV RNA at the end of treatment (Table 1). Among the non responders (16) from district Swabi who were given an extra dose of IFN and Ribavirin, (88%) were negative and only (12%) were positive for HCV RNA after 2 months additional treatment.

Discussion

Due to unhygienic conditions, poverty and low awareness regarding the spread and consequences of Hepatitis C, this infection is increasing alarmingly throughout the province. At a district level as no study had been conducted to figure out response of IFN based therapy in chronic HCV patients therefore, we now has focused three districts, district Swabi, Bunir and Kohat.

To eradicate HCV from the infected individuals, IFN- based therapy is considered as the choice of treatment throughout the world [7]. IFN alone was used to treat the patients in early days but due to more chances of relapse and failure to decrease HCV RNA, it was not considered as the successful choice of therapy. In order to overcome the problem, Ribavirin was used as an adjunct with IFN to treat hepatitis C patients. The use of the IFN and Ribavirin combination therapy led to the increase in SVR rate by 40-45% than that of IFN alone [15].

ETR (response of IFN after six months of treatment intake) of standard IFN and Ribavirin combination therapy, determined among chronic HCV patients in different districts of KPK was 81% and the resistance was 19%. High ETR was found in district Swabi (92%), followed by district Kohat (80%) and district Bunir (71%). The adverse effects during and after the therapy were also noted. The most adverse conditions observed were fatigue, headache, fever and alopecia (Table 2).

In the selected three districts of KPK, the response of combination IFN therapy was almost similar to the response studies already done in Pakistan [11,12] as well as internationally [16-18]. As the response to IFN-based therapy has been linked with age, sex and ethnicity of the affected individuals [19]. Therefore similar response of the current study indicates the presence of these favorable factors.

In district Swabi, earlier IFN response study was not conducted and we for the first time determined response of IFN combination therapy in this district. ETR rate in district Swabi (92%) was comparatively higher than the other districts (Table 1). High ETR rate in this district might be due to favorable factors like age groups, ethnicity and female sex. The most enrolled patient's age groups in district Swabi were less than 40 years (Table 3). It has been studied that patient's age lower than 40 years are more responsive to IFN therapy than age more than 40 years [19].

Beside this, the second favorable characteristic of the enrolled patients to IFN therapy was the female sex. In the studied population, the proportion of the females was more than that of male in district Swabi as compared to other districts (Table 1). It has been found that female sex is more responsive to IFN therapy than the male [19]. Therefore the response rate was found high in this district.

The ETR rate in case of district Kohat (80%) was comparatively lower than that of district Swabi (92%) and higher than that of Bunir (71%) (Table 1). Comparatively lower ETR rate might be attributed to more proportion of male sex, patient's age more than 40 years compared to that of district Swabi (Table 3).

In district Bunir, the ETR rate was very low from both of the districts Swabi and Kohat (Table 1). ETR rate was already calculated in this district which was lower than the current study [13]. This lower ETR rate compare to other districts might be due to the more number of male populations, age more than that of 40 years (Table 3) and might be due to the difference in ethnicity.

Among the non responders from district Swabi, who did not respond to standard six months therapy, when treated with an additional two months therapy with same IFN but with a high dose of

Adverse effects	Adverse effects (%)
Fatigue	55-60
Fever	30-54
Headache	51-57
Nausea	32
Dyspnea	22
Alopecia	31-33

Table 2: Commonly observed side effects with IFN and Ribavirin treatment.

Districts	Total Samples	M/F age groups	% ETR
Swabi	198	M>40=18, F>40=14 M<40=79, F<40=87	92
Bunir	89	M>40=26, F>40=21 M<40=25, F<40=17	71
Kohat	54	M>40=12, F>40=11 M<40=16, F<40=15	80

M/F (Male/Female), ETR (End of Treatment Response)

Table 3: Age wise ETR rates in different districts of KPK.

6 MIU thrice a week and 1200 mg/day of Ribavirin daily respectively, the response rate in this additional two months therapy was 88% and the resistance was 12%. It has been shown that by keeping the dose of IFN high, the patients were able to show more response. It has also been shown that IFN dose [20] and duration of treatment [21] have greater importance in long term response to antiviral therapy. Therefore response of IFN- based therapy can be enhanced by some modifications. Like SVR rates of 44% and 28%, reported by Sánchez-Tapias et al. [22] with 72 weeks and 48 weeks of treatment, respectively. From this it is clear that by increasing dose and duration of IFN, SVR can be enhanced in slow virological responders especially in HCV 1 infected individuals. This has also been proved by viral kinetics that some time viral reduction occurs rapidly with an initial dose of IFN followed by accelerated increase in viral RNA [23]. At this time it might require continuous and high dose of IFN to suppress the viral RNA as is done by Peg-IFN, which due to its prolonged action keep the viral RNA suppressed. Guidelines regarding retreatment of non responders suggest that some considerations should be considered like severity of disease, adherence/compliance, previous treatment history, tolerance issues, viral genotypes and predictive value in response [7]. Hence it is proved that slow responders get relief with some additional course of IFN combination therapy.

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