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Optimal Utilization of Prime Minister Funds for Treatment of Hepatitis C

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ABSTRACT

Hepatitis C virus infection is one of the major causes of chronic liver diseases throughout the world. In Pakistan, 10 million people are presumed to be infected with this disease. Hepatitis C virus has been characterized by having a higher rate of spontaneous mutation that leads to a marked degree of heterogeneity among its genotypes. HCV genotype plays an important role in the management of chronic hepatitis C. Knowing the genotype helps to decide about the duration, as well as to predict the response to treatment. But it is an expensive test, and not affordable for majority of patients. HCV RNA by PCR testing is advisable at various stages during the therapy. Early viral response (EVR) is to check the HCV RNA by PCR at 12 weeks, End of treatment response (ETR) is to do the testing at the end of treatment, while Sustained viral Response (SVR) means HCV RNA by PCR testing six months after completion of therapy. All these tests i.e. HCV genotype, EVR, ETR and SVR were checked in these patients. **Aims & Objectives:** The primary objective is to evaluate the proper utilization of Government funded program for the treatment of hepatitis C. Also it was aimed to determine the type of HCV genotypes as well as sub-type in chronic hepatitis C patients, to check EVR, ETR and SVR in these patients, and to evaluate the cost effectiveness of these tests. A total of 1000 patients of hepatitis C virus were recruited. **Results:** Out of 1000 patients, 506 (50.6%) were males, while 494 (49.4%) were females. The age ranged from 16 to 67 years with a predominantly larger proportion of younger patients. HCV genotype was checked in 295 patients Genotypes 1, 2, 3, mixed and untypeable were found in these patients. The predominant genotype was 3 (84%) and its subtype 3a (71%). Early Viral Response (EVR) was checked in 142 (14.2%) patients; it was achieved in 97 patients. End of treatment response (ETR) was checked in 609 (60.9%) patients, it was achieved in 405 (66.50). HCV RNA reports to confirm the SVR were available for only 60 (6%) of patients. Out of these 60, SVR was achieved in 46 (76.66%). **Conclusion:** Genotypes 2 & 3 were detected in almost 90%, while other types collectively detected in rest 10% of screened patients. Although 61% patients reported with HCV RNA reports at the end of treatment, but only 6% patients opted for follow up HCV RNA by PCR testing to look for SVR. Considering the huge cost of treatment of from government funds, measures should be adopted to have a structured program for proper evaluation of these patients before, during and after the treatment. Because of its financial implications, genotype testing is not advisable for naïve patients of chronic hepatitis C.

Keywords: Chronic Hepatitis, Genotype, HCV, Pakistan, EVR, ETR, SVR.

INTRODUCTION

Hepatitis C virus (HCV) is the major public health problem and it is one of the most important causes of chronic liver diseases all over the world. Studying the epidemiology of such problematic virus plays an important role on the methods of its prevention and treatment[1-4].

In Europe and North America the prevalence of HCV is about 1%[5, 6]. This is even higher among Southern Italy and Southern Spain varying between 8.4-22.4%. In North Africa and Arabian countries

like Libya, Tunis and Saudi Arabia the prevalence is between 1.4 and 2.1%, though it was the highest in Egypt reaching up to 19.3%[7, 8].

Pakistan is a developing country of 170 million people with low health and educational standards. According to the human development index of the United Nations, it ranked 134th out of 174 countries[9]. In Pakistan, approximately 10 million people (6%) are presumed to be infected with HCV[10].

Hepatitis C virus is characterized by a higher rate of spontaneous mutation that leads to a marked degree of heterogeneity among its genotypes[11]. The genus hepacivirus consists of 6 phylogenetically distinct clades (genotypes) from 1 to 6 and more than 70 subtypes (termed a, b, c, d etc.) of HCV[11, 12].

The epidemiology of such genotypes has been variable among different geographical regions worldwide. However, HCV genotypes 1, 2 and 3 are commonly distributed all over the world though 4, 5 and 6 were mainly found in a certain areas. HCV genotype 4 is particularly prevalent in Northern and Central African countries particularly Egypt, whereas HCV genotype 2 is more frequent in West Africans countries. Genotypes 5 and 6 are common in South Africa and Asia respectively[13].

The cumulative data of various studies done in Pakistan revealed Genotype 3 as the most common genotype (80%) followed by Genotype untypeable (16%) and genotype 1 (6%)[14-21]. In 1997, it was reported in a small study that 87% of the individuals in Pakistan[22] had genotype 3. In 2004, a panel of 30 top gastroenterologists of the country met at a conference and reported that 75-90% of HCV patients in Pakistan[10] had genotype 3a, Qazi *et al.*[23] reported in 2006 that 71% of patients had genotype 3 while only 10% had genotype 1. In 2007, it was reported that 81% of individuals had genotype 3 while only 9.5% had genotype 1[24]. Hakim *et al.* reported in 2008 that 51% of HCV patients had genotype 3a, 24% had 3a/3b co-infection and 16% had genotype 3b, while similar results were also reported by Afridi *et al.*[25] who stated that 50% of HCV patients had genotype 3a followed by 3b and 1a. The most detailed study was conducted by Idrees and Riazuddin in 2008 who performed genotyping of 3,351 patients and reported that genotype 3a was the most prevalent genotype in Pakistan[26].

HCV RNA by PCR testing both qualitative and quantitative is advisable at various stages of interferon plus Ribavirin treatment of hepatitis C. Various terminologies are now in use in accordance to the timinig of the test. These are:

- Rapid Viral Response (RVR): To check the HCV RNA by PCR after 4 weeks treatment.
- Early Viral Response (EVR): To check the HCV RNA by PCR after 12 weeks treatment.
- End of Treatment Response (ETR): To check the HCV RNA by PCR after completion of treatment.
- Sustained viral Response (SVR): To check the HCV RNA by PCR 6 months after completion of treatment.

AIMS AND OBJECTIVE

The primary objective is to evaluate the proper utilization of Government funded program for the treatment of hepatitis C. Also it was aimed to determine the type of HCV genotypes as well as sub-type in chronic hepatitis C patients, to check EVR, ETR and SVR in these patients, and to evaluate the cost effectiveness of these tests.

PATIENT POPULATION

All the patients who reported to Hepatitis Clinic, Department of Gastroenterology-Hepatology, Sheikh Zayed Federal postgraduate Medical Institute, Lahore. The patients were registered at Out Patient Department from November 2006 to May 2008 for treatment from 'Prime Minister National Program for the prevention and control of Hepatitis C' and fulfilling the criteria were inducted. A total of 1000 patients of Chronic hepatitis C were recruited.

Statistical analysis

SPSS version 17 was used to analyze the data. Quantitative variables were expressed as mean, minimum, maximum and range. Differences in proportion of qualitative variables were tested with non-parametric tests. Chi-square test and a p value <

0.05 were considered significant.

RESULTS

A total of 1000 patients were studied during a 24 months period from November 2006 to November 2008 as shown in Table 1. Out of 1000 patients, 506 (50.6%) were males, while 494 (49.4%) were females with a male; female ratio (1:1). The age ranged from 16 to 67 years with a predominantly larger proportion of younger patients with an average of less than 40 years with no significant gender variation ($P > 0, 05$).

Table 1: Age and sex distribution.

Sex	N	Minimum Age (Years)	Maximum Age (Years)	Mean Age (Years)
Male	506	16	65	34.81
Female	494	18	67	38.08
Total	1000	16	67	36.09

HCV genotype was checked in 295 patients Genotypes 1, 2, 3, mixed and untypeable were found in these patients. The predominant genotype was 3 (84%) and its subtype 3a (71%). Genotype 4, 5, 6 were not reported.

Table 2: Genotype.

	Frequency	Percent	Valid Percent	Cumulative Percent
∗GT-1	1	0.3	0.3	0.3
1a	1	0.3	0.3	0.7
1b	2	0.7	0.7	84.4
∗GT-2	19	6.4	6.4	90.8
∗GT-3	3	1.0	1.0	1.7
3a	209	70.8	70.8	72.5
3b	33	11.2	11.2	83.7
Untypeable	18	6.1	6.1	96.9
Mixed	9	3.1	3.1	100.0
Total	295	100.0	100.0	

∗GT- Genotype

Different HCV genotypes were found among the patients studied as shown in Table 2. These include genotypes, 1, 2, 3, mixed and untypeable, while HCV genotype 4, 5 & 6 were not reported among these patients. The prevalence of such genotypes was variable among the patients, Genotype 3 was the most frequent one detected in 245 (83% patients) followed by genotype 2 in 19 (6.4%) and untypeable in 18 (6.1%) patients, then mixed genotypes and genotype 1 accounted for 9 (3.1%) and 2 (0.6%) patients respectively.

The prevalence of gender associated HCV genotypes was analyzed among the patients. The most frequent genotype reported among both male and females was genotype 3 as it accounted for 118 (79.72%) and 127(86.39) of male and female patients respectively, followed by genotype 2 which accounted for 11 (7.43%) and 8 (5.44%). The untypeable genotype was noted in 12 (8.10%) males and 6(4%) female patients, while mixed type was reported in 4 (2.70%) males and 5 (3.40%). Genotype 1 is detected in 3 (4.4%) male and 1 (1.47%) female patients. The relationship between HCV genotype and gender was statistically not significant (P value >0.05).

Table 3: Genotype.

Genotype	Male	Female	Total
1	3	1	4
2	11	8	19
3	118	127	245
Untypeable	12	6	18
Mixed	4	5	9
Total	148	147	29

Table 4: Sub – types.

Subtypes	Male	Female	Total
1	1	0	1
1a	1	0	1
1b	1	1	2
2	11	8	19
3	2	1	3
3a	93	116	209
3b	23	10	33
Untypeable	12	6	18
Mixed	4	5	9
Total	148	147	29

Different sub-genotypes were also reported among the patients studied. Genotype 3a was among

the frequent as it accounted for 209 (70.8%) with predominance in females 116 (78.91), while found in 93 (62.83%) male patients (p value <0.05). The genotype 3b accounted for 33 (11.18%) patients with 23 (7.8%) males and 10 (3%) females. HCV genotype 1a accounted for only 1 (0.33%) male patient, while 1b was detected in 1(0.33%), each in both male and female patients. (Table 4)

Early Viral Response (EVR) was checked in 142 (14.2%) patients; it was undetected in 97 (68.30%) and was detected in 45 (31.70%) patients (Table 5).

End of treatment response (ETR) was checked in 609 (61%) patients, it was negative in 405 (66.50%), while it was detected in 204 (32.5%) patients. In 3919 (39%) patients reports were not available (Table 5).

HCV RNA reports to confirm the SVR were available for only 60 (6%) of patients. Out of these 60, SVR was achieved in 46 (76.66%) while SEV RNA was detected in 14 (23.34%) patients (Table 5).

Table 5: EVR-ETR-SVR.

	EVR	ETR	SVR
Detected	45	204	14
Not detected	97	405	46
Not available	858	391	940
Total	1000	1000	1000

In 72 patients, both EVR and ETR achieved while in 29 patients both EVR and ETR not achieved. In 14 patients, where EVR was not achieved, ETR was achieved. In 11 patients, where EVR was achieved, ETR was not achieved while in 16 patients where EVR was done, ETR reports were not available (Table 6).

Table 6: EVR vs ETR

HCV RNA qualitative		ETR			Total
		detected	not detected	not available	
EVR	Detected	29	14	2	45
	Not detected	11	72	14	97
	Not available	164	319	375	858
Total		204	405	391	1000

Out of 60 patients in whom SVR reports were available, relapse was seen in 10 patients and 3 patients were non – responders. SVR achieved in 44 patients (p value < 0.05), while 940 patients did not turn up for follow-up visits (Table 7).

Table 7: ETR vs. SVR

		SVR			Total
		Positive	Negative	Not available	
ETR	Detected	3	1	200	204
	Not detected	10	44	351	405
	Not available	1	1	389	391
Total		14	46	940	1000

Data shows that out of 44 patients achieved SVR, 23 (50%) were those who had also achieved EVR (Table 8).

		SVR			Total
		Positive	Negative	Not available	
EVR	Detected	2	1	42	45
	Not detected	2	23	72	97
	Not available	10	22	826	858
Total		14	46	940	1000

DISCUSSION

As far as genotype is concerned, the results of our study are not much different from other studies done in Pakistan. The predominant genotype is 3 with majority of the patients having sub-type 3a. The other issue is of both untypeable and mixed types. In the international data, no such types have been reported. It might be possible that the method of testing for genotype is not sensitive to detect other genotypes like 4, 5, 6 etc and the report has been labeled as untypeable or mixed type. The importance of knowing the genotype is to decide about the duration of treatment and to predict the response. So, assuming that these patients have genotypes other then 2 & 3, the patients having mixed, untypeable or genotype 1, one year therapy was advised.

The larger proportion of patients, 90% of the total, with genotype 2, 3 or its sub-type needs to be treated for 6 months. Keeping in view the financial constraints of Prime Minister National program and

limited resources, genotype determination in naive patients of Chronic Hepatitis C is therefore not recommended.

The other part of this study was to monitor the response of interferon and ribazole therapy by checking HCV RNA by PCR at various stages of the treatment. Initially patient follow the instructions and EVR being checked, but later on patients denied the advice because of being non-affording. The government offered these tests from certain laboratories, but because tremendous workload these laboratories fail to deliver the reports in time. So it was then decided to check the ETR, but again only 61% patients came for the follow up visit. Another problem which we faced was to get data for determination of SVR. Only 6% patients reported to outdoor. Although the SVR was around 73% in these patients, but the data was scanty and no recommendation can be made on its basis.

It was observed that the program was started without proper planning and there was lack of coordination between the various departments. It did not help in effective treatment, rather it increased the pool of non-responders and relapser patients of hepatitis C, in whom the response rate to re-treatment is quite low as compare to naïve patients, and also will now require expansive treatment i.e. pegylated interferon for possible cure.

The source of infection mainly through the blood transfusion and needle stick injury. Although, we did not gather significant data regarding previous exposure, it seems that the spread of HCV infection is mainly through the use of improperly sterilized instruments, transfusion of unscreened blood and reuse of syringes in medical practice. Therefore, measure should be taken for the prevention of spread of it.

CONCLUSION

Chronic hepatitis C is a deadly disease and number of newly diagnosed patients has increased over last few years. Genotypes 2 and 3 dominated the screening results, found in 90% of the patients. According to the international recommendations, 6 months interferon and ribavirin treatment is advisable for both the genotypes. As genotype testing is an expensive test, not afforded by majority of people, the consumption of allotted limited Government resources for this test in naive Chronic Hepatitis C patients is not recommended. Furthermore, measures should be adopted to have a structured program for proper evaluation of these patients before, during and after the treatment. Also ensure the sterilization of surgical instruments, properly screened blood transfusion and encourage use of disposable syringes in the clinical practice. *Prevention is indeed better than cure.*

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