Hepatitis C, A Mega Menace: A Pakistani Perspective

Muhammad Umar, Mohammad Bilal

[1]Chair, World Gastroenterology Organization (WGO) Hep C Guidelines Committee; Governor, American College of Gastroenterology; Professor of Medicine, Rawalpindi Medical College, Pakistan [2]Army Medical College, Rawalpindi, Pakistan

Conflicting Interest: None Declared

This article has been peer reviewed.

Article Submitted on: 12th January 2012

Article Accepted on: 15th March 2012

Funding Sources: None declared

Correspondence to: Muhammad Bilal

Address: Army Medical College, Rawalpindi

Email: billa17@hotmail.com

ABSTRACT

About 10 million Pakistani population is infected with Hepatitis C virus (HCV). The prevalence is even more pronounced among high risk population. The commonest mode of transmission is the use of injections, unsterilized needles and contaminated instruments. Combination of standard interferon and ribavirin is still the first line therapy with sustained viral response (SVR) up to 40-50%. Pool of relapsers and non-responders is increasing in Pakistan and needs treatment with pegylated interferon plus ribavirin (peg IFN/RIB). Pegylated interferon has limited use due to being costly. Efficacy of pegylated interferon in genotype 3 is still debatable. HCV related end stage liver disease and hepatocellular carcinoma (HCC) is a major cause of morbidity and mortality in health care settings of Pakistan causing exponential burden on financial health care resources.

Key Words: Hepatitis C, Interferon, Ribavirin, Prevalence

INTRODUCTION

The World Health Organization (WHO) had estimated that 180 million people are infected with Hepatitis C virus in 2009. Three to four million people get newly infected each year. Two third of these newly infected cases develop chronic liver disease [1].

HCV infection is responsible for 60-70% of all liver cancer cases and is the commonest cause of liver transplant all over the worldwide [1]. Liver cirrhosis is the 18th commonest cause of mortality [2]. HCV related liver cancer is the 8th common cancer worldwide. HCV infection prevalence varies from country to country. The global prevalence of HCV infection is 2.2 to 3% [3]. In the US and European countries, prevalence is 1.6 to 1.8% and 1 to 2.3%, respectively [4].

Pakistan is the 6th most populous country in the world with an estimated population of 16,094,3000. Prevalence of HCV infection reported in various studies by the Pakistani authors ranges from 2.2-14% [5]. Accordingly, approximately 10 million people in Pakistan are infected with HCV [6]. Within Pakistan, the HCV prevalence rate varies between the four provinces; prevalence rate reported in Punjab is 6.7%, in Sindh 5%, in Baluchistan 1.5%, and in Khyber Pakhtunkhwa 1.1% .

The prevalence of the HCV antibody positivity high risk groups (such as patients on chronic hemodialysis, health care workers, and thalassemia or hemophilia patients) is 38% to 55%. The comparison of prevalence and anti-HCV positive cases with neighboring countries of Pakistan is demonstrated in Table 1.

RISK FACTORS FOR TRANSMISSION

Injudicious use of injections had been reported as a major risk factor for HCV infection in Pakistan [9]. Luby et al reported in their study from Hafizabad, Punjab that HCV infected patients had received five or more injections in the past 10 years compared to non-infected persons [10]. In another study, Pasha et al reported that the household members who had more than 4 injections per year were 11.9 times more likely to get HCV infection than others [11]. Shazi L et al in 2006 reported injection use as a major mode of transmission of Hepatitis C [12].

Injection drug users (IDUs) were even at high

Country	Year	Population	Number	Prevalence (%)
Myanmar	2006	Healthy Adults	362	2.5
India	2003	Blood Donors	28,956	0.66
Nepal	2004	Healthy Adults	103	1.0
Iran	2006	Healthy Adults	1721	0.87
Afghanistan	2006	Healthy Women	4452	0.31
Pakistan	2009	Healthy Adults	178,322	4.7

Table 1: Comparison of HCV frequency with neighboring countries of Pakistan [15]

Patient group	Number of subjects	Positive	Percentag of positive
Liver disease	13745	7821	56.9
General blood donors	808872	21938	2.71
Adult screening	123144	7747	6.29
Hospital based studies	25746	1523	5.91
Children	6389	118	1.84
Contacts of HCV infected patients	1010	218	21.58
Renal failure	613	194	31.64
Thalassemia patients	876	387	44.17
Community prevalence	16651	1919	11.52
Ante-natal screening	1400	98	7
Health care workers	676	38	5.62
Professional blood donors	1529	159	10.39
Injection drug users	562	489	87.01
Hemophilia patients	240	122	50.83
Other*	2938	211	7.18
Total	1004391	42982	4.27

** Lymphoproliferative disorder patients, prisoners, depressed patients, mothers and sex workers.*

Table 2: Details of anti–HCV antibody status in Pakistani population [16]

risk of acquiring HCV infection. In studies conducted by Kuo et al in Lahore and Quetta in 2003, HCV prevalence rate was 93% and 75% in IDUs. Other risk factors for the transmission of HCV infection were injections given by health care workers, sex workers as well as household contacts. In health care workers, HCV prevalence rate was 5.5-6%, which is less than the community [11].

In Pakistan, a large segment of rural population goes to barbers for facial shave. Quite often barbers use razors that are not disposable, possibly contaminated, and often reused for shaving without proper disinfection. Janjua et al reported that only 13% people knew that hepatitis can be transmitted by contaminated razors. There is no cohort study to prove the exact risk of transmission of HCV infection with contaminated razors, scissors and other instruments used by salon workers.

Transmission of HCV in household contacts as well as within families is not well documented in Pakistan. A study by Portic et al showed that the prevalence of HCV in household contacts of HCV families was 2.5 times that of the general population [12].

BURDEN OF HCV RELATED CHRONIC LIVER DISEASE

In Pakistan, major cause of liver disease is HCV infection. As HCV infection has high chronicity rate, it leads to an increase burden of chronic liver disease with its complications. About 10 million people harboring HCV infection are at risk of developing some form of complication, such as cirrhosis, hepatic encephalopathy, variceal bleed, hepatocellular carcinoma or liver

YEAR	TOTAL ADMISSIONS	LIVER DISEASE RELATED ADDMISSIONS (n)	% OF LIVER DISEASE ADMISSIONS
1998	1267	279	22%
1999	2104	483	23%
2000	2139	571	26%
2001	2587	646	25%
2002	2546	601	23%
2004	1036	312	30%
2005	1930	579	30%
2006	3595	1263	35%
2007	2200	587	27%
2008	2655	732	28%
2009	2407	609	24%
2010	2692	779	29%

Table 3: Total and liver disease related admissions over 9 years (1998-2010) [13]

YEAR	TOTAL NO. OF DEATHS	LIVER DISEASE RELATED DEATHS (Number)	LIVER DISEASE RELATED DEATH (Percentage)
1998	315	115	37%
1999	322	70	22%
2000	359	89	25%
2001	377	75	20%
2002	346	62	21%
2004	210	62	30%
2005	352	102	24%
2006	397	110	28%
2007	390	120	31%
2008	587	88	15%
2009	654	223	34%
2010	694	410	59%
TOTAL	5003	1526	30.50%

Table 4: Annual death and liver disease related mortality [13]

related death. There is no formal registration of hepatitis patients in Pakistan. However, hospital based data has shown that every 4th patient admitted in medical ward has liver related disorders. HCV related liver disease is one of the commonest cause of death in Pakistan. A study published from our department showed that out of 21999 patients admitted in medical department past 9 years (1998-2008), 6053 (27.51%) patients were with liver disease. Average patients admitted per year were 2205±725. 3655 patients died (16.61% of total admissions in 9 years);

Author (Year)	Place	Number	ETR%	SVR%
Hussain AB (2000)	Rawalpindi	204	72.40%	-
Shaikh WM (2002)	Larkana	82	71%	65.40%
Farooqi JI (2002)	Peshawar	183	88%	82.61%
Khokhar N (2002)	Islamabad	100	83.00%	79.50%
Niaz A (2003)	Rawalpindi	60	75.00%	-
Hussain AB (2004)	Rawalpindi	279	86.50%	76%
Muhammad N (2004)	Buner	350	85.14%	78.85%
Farooqi RJ (2005)	Swat	33	M=77.27% F= 81.81%	M= 61.18% F= 72.27%
Farooqi JI (2005)	Peshawar	65	M=86.04% F= 86.36%	M= 81.39% F= 86.36%
Sarwar S (2005)	Lahore	55	-	56.30%
Qureshi S, Batool U(2006)	Islamabad	250	81.00%	58.90%
Khan A (2009)	Lahore	721	-	72.7%
Hepatitis Prevention & Control Program (2008) (Holy Family Hospital) (unpublished data)	Rawalpindi	300	75%	50%

Table 5: End treatment response and sustained virological response with standard IFN/RBV combination therapy in chronic hepatitis C [15]

24.43% (n=993) of these were liver related deaths. 893 liver related deaths were noted annually [13]. Approximately half of these liver related deaths can be attributed to HCV, but keeping in mind the limitations of the study as PCR or RIBA was not done to confirm the HCV status.

TREATMENT RESPONSE OF CHRONIC HEPATITIS C PATIENTS

In Pakistan, the commonest genotype is 3a.15 Genotype 2 and 3 are considered easy to treat as compared to genotype 1. Being cheap, standard interferon plus ribavirin combination therapy is to be considered the first line treatment for chronic hepatitis C patients.9 This combination has been used in Pakistan since 1998. Different authors have reported different treatment responses from different centers. Details of end-of-treatment response (ETR) and sustained viral response (SVR) are shown in Table 5. SVR in patients treated with conventional interferon and ribavirin ranges from 50 to 81%. One limitation of these studies was that all the viral responses were not checked uniformly. Secondly, the data analysis methods were not clearly defined; either the treatment responses were analyzed as intention to treat (ITT) analysis or per-protocol (PP) analysis. This resulted in great variation particularly in SVR. That is one possible explanation in varying of SVR from 50 to 81% in different national studies shown in Table 5.

Regarding pegylated interferon, limited data is reported. One study of 73 patients by Khan et al showed an SVR of 85% from Lahore [18]. We analyzed data of 300 patients at our department (Liver Research Clinic, Holy Family Hospital, Rawalpindi, Pakistan) treated with conventional interferon and ribavirin as PP analysis. The results showed a rapid virological response (RVR) 68.9%, early virological response (EVR) 77.6%, ETR 70.9% and SVR 63.2%. Similarly, analysis of 227 patients from our department treated with pegylated interferon and ribavirin showed RVR 68%, EVR 75.8%, ETR 76.6% and SVR 60.5%.

We conclude two important points from our data analysis. One being that the treatment responses in patients treated with pegylated interferon and ribavirin are comparable to patients treated with conventional interferon and ribavirin. Secondly, the SVR achieved in patients treated with pegylated interferon and ribavirin even in genotype 2 and 3 is much lower than that

reported in international studies [19,20]

Based on our data and other national studies, Pakistan Society of Gastroenterology and GI Endoscopy recommended that in Pakistan, the first line therapy for genotypes 2 and 3 patients should be conventional interferon and ribavirin and only non-responders and relapsers to conventional interferon and ribavirin should be treated with pegylated interferon and ribavirin [15]. This will be the cost effective approach.

IMPLICATIONS OF COST OF ANTIVIRAL THERAPY

There is no reimbursement or health insurance system in Pakistan. Mostly patients and their family pay for the treatment. Six months treatment with standard interferon and ribavirn cost about US$500 for drugs and US$200 for the follow-up and investigations. Treatment with pegylated interferon and ribavirin costs around US$4000. Considering the emerging data of equal response rates in genotypes 2 and 3, Pakistan Society of Gastroenterology and GI Endoscopy and Pakistan Society of Hepatology National Consensus Guidelines 2009 had recommended standard interferon and ribavirin as the first line therapy for HCV genotypes 2 and 3 patients in Pakistan.[15] Pegylated interferon and ribavirin should be reserved for non-responders and relapsers of standard interferon and ribavirin therapy as well as in individualized cases.

DISCLOSURE

The tables in this article have been reproduced after permission from Pakistan's Journal of Gastroenterology and Journal of College of Physicians and Surgeons Pakistan. A proof of the permission is available for review of the editorial board of JPMS.

REFERENCES

1. World Health Organization. Hepatitis C. Available at: www.who.int/vaccine_research/viral_cancers. Retrieved on 16-04-2009.
2. World Health Statistics. Geneva: World Health Organization.2008.
3. Lavanchy D. The global burden of hepatitis C. Liver Int 2009; 29(Suppl 1):74-81.
4. Marcellin P. Hepatitis B and C in 2009. Liver Int 2009; 29 (Suppl 1):1-8.
5. Sy T, Jamal MM. Epidemiology of hepatitis C virus (HCV) infection. Int J Med Sci 2006; 3:41-6.
6. Raja NS, Janjua KA. Epedemiology of hepatitis C virus infection in Pakistan. J Microbiol Immunol Infect 2008; 41:4-8.
7. The world factbook. Pakistan. USA: Central Intelligence Agency. 2007. [accessed August 2008]. Available at: https://www.cia.gov/library/publications/the-world-factbook/geos/pk.html
8. California state facts. United States Geological Survey. 2006. [accessed August 2008]. Available at:http://www.usgs.gov.
9. Hauri AM, Armstrong GL, Hutin YJ. The global burden of disease attributable to contaminated injections given in health care settings. Int J STD AIDS. 2004;15:7–16.
10. Luby SP, Qamruddin K, Shah AA, Omair A, Pahsa O, Khan AJ, et al. The relationship between therapeutic injections and high prevalence of hepatitis C infection in Hafizabad, Pakistan. Epidemiol Infect. 1997;119:349–56.
11. Pasha O, Luby SP, Khan AJ, Shah SA, McCormick JB, Fisher-Hoch SP. Household members of hepatitis C virus-infected people in Hafizabad, Pakistan: infection by injections from health care providers. Epidemiol Infect. 1999;123:515–8.
12. Shazi L, Abbas Z. Comparison of risk factors for hepatitis B and C in patients visiting a gastroenterology clinic. J Coll Physicians Surg Pak. 2006;16:104–7.
13. Ambreen S, A. Mohammad, Umar M, et al, Nine Year Audit Liver Disease burden and Liver related mortality Audit in Tertiary Care Hospital of Rawalpindi Medical College. Pak J Gastroenterol Oct 2008; 22:31-34.
14. Khokhar N, Niazi S. Chronic Liver Disease Related Mortality Pattern in Northern Pakistan. J Coll Physicians Surg Pak 2003; 13:495-7.
15. Umar M, Khaar HB, Khan AA, et al. Diagnosis, Management, and Prevention of Hepatitis C in Pakistan. Pak J Gastroenterol 2009; 23:8-19.
16. Umar M, Khaar HT, Khurram M, Hasan Z. Anti-HCV Antibody Positivity of Various Sections of Pakistani Patients. J Coll Physicians Surg Pak. 2009; 19:737-41.
17. Umar M, Bushra H, et al. Hepatitis C in Pakistan: A review of available data. Hepatitis Monthly 2010; 10:205-214.
18. Khan AA, Sarwar S. Response to combination therapy in Hepatitis virus C genotype 2 and 3. J Coll Physicians Surg Pak 2009; 19:473-7.
19. 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.
20. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL Jr, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002; 347:975–982
21. Batool U, Qureshi S. Declining sustained virological response in hepatitis C. J Coll Physicians Surg Pak 2006; 16:187-91.