ORIGINAL ARTICLE

Treatment of hepatitis B and C through National Programme — An audit

Huma Qureshi,[1] Bile Khalif Mohamud,[2] Syed Ejaz Alam,[3] Ambreen Arif,[4] Waquaruddin Ahmed[5]

Abstract

Objectives: To evaluate the response to treatment given on a large scale for hepatitis B and C through a nationwide programme.

Methods: Records of patients who received treatment of hepatitis B and C during past 2 years through the Prime Minister's programme for the Prevention and Control of Hepatitis Viral Infection was retrieved randomly from 12 sites after taking consent from the management and the site managers. Data confidentiality was ensured. All data was photocopied and brought to the Pakistan Medical Research Centre at the Jinnah Postgraduate Medical Centre, Karachi, where it was entered and analysed. The inclusion/exclusion criteria and the followup tests that were to be done before, during and after treatment were taken from the National programme manager so that actual data could be matched with the guidelines. Data was analysed through a specially developed programme.

Results: A total of 7752 patients received treatment at the 12 sites for hepatitis C. Adherence to inclusion/exclusion criteria or protocol was followed in 7572 (97.6%) patients. Out of 7572 patients, 3440 (45.4%) completed 6 months of interferon therapy, but the polymerase chain reaction test at the end of 6 months was available in 1686 (49%) cases. It was not detected at 6 months in 1133/1686 (67%) cases, while in 553 (33%) cases there was no response. Data for hepatitis B was collected from 8 sites. A total of 454 cases received treatment and 85 (18.72%) fulfilled the inclusion criteria. Treatment was completed by 9 (10.58%) cases, with 3 (3.52%) cases showing Hepatitis B 'e' antigen clearance and anti-HBe (antibody to hepatitis B 'e' antigen) production.

Conclusion: Poor followup and inadequate documentation of serological/biochemical tests were the major drawbacks in both hepatitis B and C patients, resulting in wastage of huge human and financial resources without proper planning and accountability.

Keywords: Hepatitis B and C, Viral Infection, Pakistan Medical Research Centre, JPMC. (JPMA 63: 220; 2013)

Introduction

Hepatitis B and C are common causes of viral hepatitis in Pakistan. Meta analysis from the previous studies showed that the prevalence of hepatitis B was between 3-4%[1] and for hepatitis C it was between 4-6%,[2] giving an overall 10% prevalence of the two viral diseases.[3] A recent survey showed the prevalence of hepatitis B (HBV) and C (HCV) as 2.5% and 5%[4] respectively with an estimated total of 12 million cases being exposed to these viruses. Higher prevalence of hepatitis C has been reported from Punjab[5] and Sindh,[6] while Sindh and Balochistan[7,8] have shown very high prevalence of hepatitis B.[9]

Genotype of hepatitis C vary worldwide and the type and duration of treatment vary according to the genotype. Since genotype 3 is the most prevalent (80%) followed by genotype 2 in Pakistan,[3,10] a treatment protocol of 3 million unit interferon, three times a week subcutaneously is recommended for 6 months along with antiviral ribavarin twice a day (weight <70 kg). For all other genotypes either pegylated or conventional interferon is recommended for 12 months. A stringent selection criteria lead to achieving best treatment response which rarely cross beyond 70% for viral clearance,[11] while 30% do not respond or relapse following cessation of therapy.[12]

Treatment of hepatitis B is more difficult as inclusion criteria and followup is dependent on sophisticated tests which are difficult to interpret by many general practitioners. Only naive cases of hepatitis B (wild type and pre-core/core mutants) with raised alanine amino-transferase (ALT) are likely to respond with nucleoside analogue-lamivudine.[13,14] The drug is to be given orally before breakfast as it is absorbed in acidic medium and treatment is to be continued till seroconversion in the wild type and almost for life in mutants, while the drug has no therapeutic role in carriers and delta infected cases.[15]

The Prime Minister's Programme for the Prevention and Control of Hepatitis Viral Infections was launched for 5 years from 2005 to 2010 to support treatment of hepatitis B and C for patients who could not afford the treatment due to high cost of medicines and diagnostics along with promoting preventive interventions. Medicines along

[1,3-5]Pakistan Medical Research Council, PMRC Research Centre JPMC Karachi, [2]Former WHO Country Representative.

Correspondence: Ambreen Arif. E-mail: ambreenarif_pmrc@yahoo.com

with diagnostics were supplied to 61 treatment sites across the country along with training of the doctors and laboratory staff on the subject and development of clear guidelines about who to treat and with what drug and dose, and how to follow them up to see response.

The present study was undertaken to evaluate how well the developed guidelines for treatment were followed and if the targets were achieved post-treatment in terms of money and workforce spent.

Patients and Methods

A total of 61 sites were providing diagnostic and treatment facilities to the patients in the four provinces of Pakistan and the federal capital. Out of these 12 sites for HCV and 8 for HBV were selected through computer-generated numbers, giving equal representation to all the regions, using provincial population figures. There were 3 sites each from Sindh and Punjab, 2 each from Balochistan and NWFP and the Federal Capital area. For confidentiality, the name of treatment sites were coded alphabetically. The consent of the programme manger and all selected site managers was taken before the start of the study. The case records of all patients treated at those sites were photocopied and brought to Pakistan Medical Research Centre (PMRC) at the Jinnah Postgraduate Medical Centre (JPMC) in Karachi for data entry and analysis in 2011. For those centers that gave a soft copy of the record, the hard copy was checked before accepting the soft copy.

The inclusion and exclusion criteria and the treatment protocols developed and printed by the programme management were taken from the programme manager for reference while evaluating the inclusion of cases and their management.

For inclusion in the treatment programme, a letter or endorsement form was required to be issued by the local government, stating that that the patient is technically recognised as eligible for treatment support and is economically poor and unable to afford the treatment cost. For hepatitis C, only patients between 18 to 50 years of age were considered eligible, provided they had a reactive anti-HCV on Enzym-linke immunosorbent assay (ELISA) along with raised ALT levels of over 1.5 times the upper limit of normal on 2 occasions 6 months apart and a detected HCV ribonucleic acid (RNA) test. Only naïve cases had to be treated with no signs of decompensation (ascites, gastrointestinal bleed, encephalopathy), and no co-infection with hepatitis B, or associated renal or cardiac failure. Injections were to be given subcutaneously three times a week along with ribavirin daily. Blood complete picture (CP) and ALT were to be done every month to see the response and drug tailoring was carried out where required (if haemoglobin fell below 8 grams or Total Leucocyte Count (TLC) fell below 1500 or platelets fell below 50,000). HCV RNA was to be tested at 6 months to confirm its non-detection and thus the response was called the end of treatment response (ETR). Sustained viral response (SVR) was the response at 12 months (6moths after the cessation of therapy), where HCV RNA were not detected with a normal ALT. ETR checking was mandatory, while SVR was optional.

The inclusion criteria for hepatitis B treatment were considered for patients older than 5 years of age, having chronic liver disease for over 6 months. Patients with raised ALT 1.5-2 times the upper limit of normal on two occasions 6 months apart with Hepatitis B 's' antigen (HBsAg) reactive and HBV-DNA detected were included in the study. Both groups were eligible for treatment i.e wild type (HBeAg reactive) and core or pre-core mutant (HBeAg non-reactive). The treatment was one tablet of lamivudine (100mg) to be taken orally before breakfast till seroconversion. During treatment for wild type, followup was to be done after every four months to check the ALT levels. HBeAg/HBV DNA were to be tested at 6 months. A negative HBV DNA along with lowering or normalisation of ALT was indicative of a response. The ALT levels continue to drop after 6 months till they reach the baseline and persist there. End point of therapy for the wild type of disease was seroconversion i.e. loss of HBeAg and appearance of anti-HBe (antibody to HBeAg). For the mutant group, non-detection of HBV DNA along with normalisation of ALT levels and their persistence to the baseline for at least a year were the end point. The exclusion criteria were HBsAg carriers (HBV DNA negative cases); those with normal ALT; and those co-infected with hepatitis C virus; Delta virus; and children less than 5 years of age.

Special data entry programme was developed for data entry and analysis. Although it was the site manager's responsibility to hand over the complete data, but still PMRC personnel were trained to understand what data to look for before photocopying it and how to check for the missing data. All efforts were made to retrieve as much data as possible without causing much inconvenience to the record holder. All data was photocopied at the treatment site and once photocopied, it was counter-checked and signed by the on-site manager before being taken by the PMRC person.

All data from these 12 sites was brought to PMRC head office from where it was sent to PMRC research centre at the JPMC, Karachi, where data entry and analysis was performed.

Results

The number of patients treated at the selected sites were 7752 for HCV (Table-1) and 454 for HBV (Table-2).

A pre-requisite for treatment support was endorsement from the member of the local government, like the Union counselor or Nazim. This letter was missing from most of the sites and only a national identity card (NIC) photocopy was attached in the file.

For hepatitis C, the adherence to inclusion and exclusion criteria and the treatment response was evaluated in all those cases who received the treatment. Out of 7752 patients who received treatment, adherence to protocol was followed in 7572 (97.6%) patients, while the remaining 180 (2.3%) cases had insufficient or missing information to justify inclusion. All patients were treated with 3 million international units (MIU) interferon thrice a week along with ribavirin,

Out of 7572 patients who received treatment, only 3440 (45.4%) cases completed 6-month interferon therapy, while the rest were lost to followup and were excluded from the final analyses. Adequate information at the end of 6 months was available at only 2 out of 12 (16.66%) sites. At 6 months, tests like ALT and PCR were available for 1686 (49%) cases and these were finally used to calculate the ETR.

As seen on normalisation of ALT and non-detected PCR at 6 months, ETR was seen in 1133/1686 (67%) cases, while the remaining 553 (33%) cases showed persistence of virus and thus were labelled as non-responders.

For hepatitis B, treatment was given to 454 cases at 8 selected sites. Adherence to inclusion criteria was met in 85 (18.72%) cases only. Using the given criteria, 54 (63.52%) cases were of wild type, and 31 (36.47%) cases core/pre-core mutant group. Followup was poor and only 9 (10.58%) cases completed treatment and 3 (3.52%) cases showed seroconversion i.e. HBeAg clearance and appearance of anti-HBe.

The records showed that drug was supplied to the patients on a monthly basis as this information was entered in the file, but reports for blood CP and ALT, PCR

Table-1: Evaluation for Hepatitis C virus.

HCV - sites	Overall	1	2	3	4	5	6	7	8	9	10	11	12
Total cases	7752	987	746	260	900	320	635	360	329	15	223	2050	927
Nos. Fulfilling inclusion criteria													
(Adults, No sign of decompensation	7572	982	727	244	871	320	538	360	329	6	222	2046	927
HCV & PCR +ve)	(97%)	(99%)	(97%)	(94%)	(97%)	(100%)	(85%)	(100%)	(100%)	(40%)	(99%)	(99%)	(100%)
Treatment:													
Completed	3440	133	278	216	871	320	14	354	329	5	114	-	806
End Point - End of 6 months ETR													
PCR Done at 6 months.	1686												
(49%)	100	3	50	602	311	14	71	115	-	16	-	404	
Non Responder : (PCR positive)	553												
(32.7%)	52	1	3	164	72	14	12	32	-	2	-	201	
Responders: (PCR negative)	1133	48	2	47	438	229	-	59	83		14		203
	(67%)	(48%)	(67%)	(82%)	(73%)	(74%)		(83%)	(72%)	-	(75%)	-	(50%)

HCV: Hepatitis C virus. PCR: Polymerase chain reaction.

Table-2: Evaluation for Hepatitis B virus.

HBV - sites	Overall	1	2	3	4	5	6	7	8
Total cases	454	35	175	30	12	37	16	76	73
Fulfilling inclusion criteria	85	22	13	2	3	7	0	21	17
	(19%)	(63%)	(7%)	(7%)	(25%)	(19%)		(28%)	(23%)
Group I (Wild type) HBeAg +ve HBV DNA +ve	54	11	8	2	3	5	-	13	12
Group II (Pre_core mutant) HBeAg -ve, HBV DNA +ve	31	11	5	-	-	2	-	8	5
Treatment: Completed (ETR)	9	6	0	2	-	-	-	1	-
HBV DNA negative, ALT normal at 1 year	3	2						1	
	(33%)	(33%)	-	-	-	-	-	(100%)	-

ETR: End of treatment response. HBV: Hepatitis B virus. DNA: Deoxyribonucleic acid. ALT: Abnine aminotransferase.

and other viral markers were missing during the therapy in most of the cases.

Discussion

The data of 7752 cases of HCV and 454 cases of HBV was retrieved who received treatment. For hepatitis C, the overall response at the end of 6 months was seen in 1133/1686 (67%) with 553 showing no response. Overall, there was non-adherence to the set criteria of inclusion, exclusion, treatment and followup. SVR was not checked as this was not the part of the project.

Studies have shown that despite picking the best cases for treatment of hepatitis C, the response rate is around 60-70%.[16-20] It is reported that patients who fail to clear the virus with the conventional interferon have only 10-15% chance of viral clearance with the pegylated interferon[15] which is 3-4 times more expensive. Therefore, every effort should be made to choose the eligible cases, treat them adequately and ensure good compliance. The response rate achieved in the present study clearly points towards a compliance issue and not the quality-of-drug issue.

Despite its modest financial resource allocations to the health sector, the Pakistan government had made a genuine and commendable effort to respond to the treatment needs of chronic HCV and HBV patients, recognising the potential high ambulatory and hospital costs and related economic burden to the national exchequer.[21] The intervention aimed also to mitigate the catastrophic out-of-pocket expenditures that the underprivileged patients and their families would have faced through the high cost of prescription drugs. The results of the present study show that proper planning, monitoring and evaluation were lacking after the project was implemented. There is a need to hold accountable those who failed to follow the guidelines.

Calculating the cost of treatment is difficult as the drugs and diagnostics were purchased in bulk, therefore their cost was substantially low. Presuming the cost of treatment to be a quarter of the standard market rates, interferon plus ribavirin cost would be Rs1500/month/patient. The cost for 6 months would be Rs9000. When multiplied by the number of patients (7572) who received treatment, it comes to Rs68 million. For HBV, the cost of one tablet daily was Rs25; so for one month the cost would be Rs1050, and for one year it would be Rs12600/patient. When multiplied by the number (454) of cases who were treated, the cost comes to Rs5.7 million. Adding these, the money spent on treatment cost comes to Rs74 million. With a few more millions for the diagnostic tests, the cost would escalate to approximately Rs100 million. The government thus spent about Rs100 million on the treatment of about 8000 cases with an ultimate response in only 1135 cases.

The ability of 2 sites to vigilantly follow the cases was able to give us the numerical figures to play with the data. It also clearly shows the commitment of these two site managers. However, the loss of over 50% recruited patients raises serious concerns and lack of commitment of the managers at the other treatment sites. The reasons of failure, like managerial issues, bad patient selection and poor compliance should have been timely assessed and rectified. Such an action would have induced significant improvements in the programme implementation and would have prevented the unjustified discontinuation of therapy, and enhance the desired good treatment response and followup to verify its sustainability.

Hepatitis B treatment through nucleoside analogues-lamivudine is recommended in a selected patient population with markers showing viral activity.[22] Response is, therefore, dependent on the right selection of cases, treatment duration and therapy compliance, as a high level of resistance is reported with this drug after one year of therapy.[23] In the present study, many cases were treated for a year without supporting markers for viral replication, thus defaulting the inclusion criteria and probably also adding to the pool of drug-resistant cases. In future, treatment of hepatitis B should be given to specialised centres to avoid the misuse of drugs that could accelerate the development of more resistant cases.

The timely treatment of chronic HBV and HCV hepatitis patients before their progression to liver cirrhosis and hepatocellular carcinoma would result in long-term cost savings for Pakistan, a country with an infection pool of about 12 million, where public health services system constitute the only source of care available for the poor. The programme for the prevention and control of hepatitis should work more and spend more on preventive interventions that would yield substantive gains to population's health with nominal to be spent on treatment. The sheer pressure from the communities and policymakers at national, provincial and district level on the highly demanded treatment component has overshadowed the wider preventive and control measures against these viral infections. In the socio-economic context of Pakistan, a nationwide intervention for the control of hepatitis viral infections would require a robust anti-viral therapy component along with proper propagation of knowledge, attitude and practices that are relevant to the prevention of these viral infections. These interventions are essential and necessary to halt the

escalating trend of HBV and HCV transmission in the country, the most effective being the promotion of safe injection practices and universal vaccination against hepatitis B.

Conclusion

To enhance its effectiveness, the HCV and HBV treatment component should be combined with other national poverty reduction, social safety activities along with strict treatment eligibility, identification and approval criteria.

Acknowledgements

We are grateful to the WHO for financial support, and, indeed, to consultants/physicians and their supporting staff at the 12 selected sites for cooperation. Mr Mahmood Ahmed and other PMRC personnel who visited the sites and collected data and those who analysed it also deserve our acknowledgement.

References

1. Andre F. Hepatitis B epidemiology in Asia, the Middle East and Africa. Vaccine 2000; 18 Suppl 1: S20-2
2. Zuberi SJ. Seroepidemiology of HBV/HCV in Pakistan. International Hepatology Communications Pakistan Medical Research Council 1996; 5: 19-26.
3. Bosan A, Qureshi H, Bile KM, Ahmad I, Hafiz R. A review of hepatitis viral infections in Pakistan. J Pak Med Assoc 2010; 60: 982-1076.
4. Qureshi H, Bile KM, Jooma R, Alam SE, Afridi HU. Prevalence of hepatitis B and C viral infections in Pakistan: findings of a national survey appealing for effective prevention and control measures. East Mediterr Health J 2010; 16 Suppl: S15-23.
5. Aslam M, Aslam J. Seroprevalance of the antibody to hepatitis C in select groups in the Punjab region of Pakistan. J Clin Gastroenterol 2001; 33: 407-11.
6. Abbas Z, Jeswani NL, Kakepoto GN, Islam M, Mehdi K, Jafri W. Prevalence and mode of spread of hepatitis B and C in rural Sindh, Pakistan. Trop Gastoenterol 2008; 29: 210-6.
7. Abdullah EM, Abdullah FE. Seropositive HBsAg frequency in Karachi and interior Sindh, Pakistan. Pak J Med Sci 2007; 23: 157-60.
8. Seven percent in Baluchistan suffer from Hepatitis B. PPI - Pakistan Press International April 10, 2004.
9. Prevalence of hepatitis B&C in Pakistan. Pakistan Medical Research Council; 2008.
10. Shah AH,Jafri W, Malik I, Prescott L, Simmonds P. Hepatitis C virus (HCV) genotypes and chronic liver disease in Pakistan. J Gastroenterol Hepatol 2008; 12: 758-61.
11. Nadeem A, Aslam M, Hussain T, Hussain MM, Khan SA. Efficacy of combined interferon alpha and ribavirin therapy in patients of chronic hepatitis C. Pak J Physiol 2007; 3: 1-3.
12. Qureshi S, Batool U, Iqbal M, Qureshi O, Kaleem R, Aziz H, et al. Response rates to standard interferon treatment in HCV Genotype 3a. J Ayub Med Coll Abbottabad 2009; 21: 10-4.
13. Dienstag JL, Schiff ER, Wright TL, Perrillo RP, Hann HW, Goodman Z. Lamivudine as initial treatment for chronic hepatitis B in the United States. N Engl J Med 1999; 341: 1256-63.
14. Rizzeto M, Volpes R, Smedile A. Response of pre-core mutant chronic hepatitis B infection to lamivudine. J Med Virol 2000; 61: 398-402.
15. Yurdaydin C, Bozkaya H, Onder FO, Sentürk H, Karaaslan H, Akdogan M, et al. Treatment of chronic delta hepatitis with lamivudine vs lamivudine + interferon vs interferon. J Viral Hepat 2008; 15: 314-21.
16. A New Era of Hepatitis C Therapy: AASLD 2010. (Online) (Cited 2010 Nov 20). Available from URL: www.medscape.com/viewarticle/732439.
17. Chronic Hepatitis C: Current Disease Management. (Online) (Cited 2010 Nov 20). Available from URL: digestive.niddk.nih.gov/ddiseases/pub.
18. Ahmed WU, Arif A, Qureshi H, Alam SE, Ather R, Fariha S, Waquar J. Factors influencing the response of interferon therapy in chronic hepatitis C patients. J Coll Physicians Surg Pak 2011; 21: 69-73.
19. Mahsud I, Khan RD, Khan M, Hameed K. Response of hepatitis C patients to alpha interferon and ribavirin combination therapy. Gomal J Med Sci 2008; 6: 65-8.
20. Yuan HJ, Lee WM. Nonresponse to treatment for hepatitis C: current management strategies. Drugs 2008; 68: 27-42.
21. McCombs JS, Yuan Y, Shin J, Saab S. Economic burden associated with patients diagnosed with hepatitis C. Clin Ther 2011; 33: 1268-80.
22. European Association for the Studyof the Liver. EASL Clinical Practice Guidelines: Management of Chronic hepatitis B. J Hepatol 2009; 50: 227-42.
23. Libbrecht E, Doutreloigne J, Van De Velde H, Yuen MF, Lai CL, Shapiro F, et al. Evolution of primary and compensatory lamivudine resistance mutations in chronic hepatitis B virus-infected patients during long-term lamivudine treatment, assessed bya line probe assay. J Clin Microbiol 2007; 45: 3935-41.