MOST PATIENTS OF HEPATITIS C VIRUS INFECTION IN INDIA PRESENT LATE FOR ANTIVIRAL TREATMENT: AN EPIDEMIOLOGICAL STUDY OF 777 PATIENTS FROM A NORTH INDIAN CENTER

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Short Title: HCV Patients in India present late for antiviral treatment

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ABBREVIATIONS

AFP	**Alphafetoprotein**
ALT	**Alanine aminotransferase**
ANA	**Antinuclear antibody**
BCLC	**Barcelona Clinic Liver Cancer**
DAA	**Directly acting agents**
FNAC	**Fine needle aspiration cytology**
HBV	**Hepatitis B virus**
HCC	**Hepatocellular carcinoma**
HCV	**Hepatitis C virus**
HIV	**Human immunodeficiency virus**
PCR	**Polymerase chain reaction**
PEG-IFN	**Pegylated Interferon**
RBV	**Ribavirin**
RNA	**Ribonucleic acid**
SMA	**Smooth Muscle Antibody**
SVR	**Sustained virological response**
WHO	**World health organization**

ABSTRACT

Background: Antiviral therapy with Peg-interferon and Ribavirin is offered only to those patients of HCV who are in stage of either chronic hepatitis or early cirrhosis. Patients of advanced liver disease do not tolerate this therapy. Since HCV is asymptomatic in early stages and usually presents late with advanced disease, the eligibility and applicability for antiviral therapy is thus limited. There are no studies from India, which look into the clinical spectrum of HCV infection at presentation, with reference to the eligibility, extent of applicability, and success of antiviral treatment in real life situation.

Aim: To study the spectrum of presentation of HCV infection, determine their eligibility for antiviral treatment, and follow those treated for treatment response.

Patients and Methods: The records of all consecutive patients of HCV, >14 years age, who presented to our department between 2008 and 2014, were analyzed for categorization into chronic hepatitis, cirrhosis and hepatocellular carcinoma; and to assess eligibility for antiviral treatment. Patients with detectable HCV RNA who have chronic hepatitis or Child A cirrhosis were considered eligible for antiviral treatment. Patients who received treatment were followed for sustained viral response.

Results: A total of 777 patients (median age 49 [range 15-95] years, males 69%) presented during the study period with chronic HCV infection. Cirrhosis was the most common presentation (56%) followed by chronic hepatitis (37%) and HCC (7%). Of patients who had cirrhosis (including those with HCC) 36% had Child A cirrhosis; 51% had Child B cirrhosis and 14% had Child C cirrhosis. Out of all the

777 HCV patients only 347 (45%) were eligible for antiviral treatment. Among the remaining 430 patients, in 326 (76%) the disease was far too advanced to offer any antiviral treatment. Of patients eligible for antiviral treatment only 54% (189/347) actually received antiviral treatment and 81% (153/189) patients could complete the antiviral course. Of them 70% (107/153) only could achieve the SVR.

Conclusions: Most patients of HCV infection in India present late and only about 45% are eligible for antiviral treatment with Peg-interferon and Ribavirin. At presentation 56% patients already have cirrhosis and 7% have HCC. Since HCV is usually asymptomatic at treatable stage, awareness about screening should be increased so that more patients are diagnosed at treatable stage.

KEYWORDS

Hepatitis C; cirrhosis; epidemiology; chronic liver disease; hepatocellular carcinoma.

INTRODUCTION

Hepatitis C virus (HCV) is a ribonucleic acid (RNA)-enveloped flavivirus, mainly transmitted by a parenteral route. HCV infection is a major public health matter of concern to countries like India (1). It is the leading cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC) the world over. It is estimated that 180 million people are infected worldwide (2), and more than half of them are not even aware of their infection (3). There are several factors influencing interactions between the host and the HCV; therefore, the clinical picture and natural history are variable for both acute and chronic hepatitis. After acute infection, 75%–85% of patients develop chronic disease (4). Chronic HCV infection often follows a progressive downhill course, and may ultimately result in cirrhosis, HCC, and the need for liver transplantation (5).

Hepatitis C is an emerging infection in India, with a paucity of large-scale prevalence studies on hepatitis C in the general population. The reported prevalence rates also vary widely (range 0.09% to 7.89%) (6). The burden of HCV infection in India is expected to be high with a population over 1.2 billion; as a result, its treatment modalities, as well as success rates, demand urgent attention (7). However, the eligibility and the success of treatment is highly dependent on the stage of presentation of HCV. The currently available antiviral treatment with Peg-Interferon and Ribavirin can only be offered to patients who have chronic hepatitis or early (Child A) cirrhosis. Patients who have advanced liver disease in form of Child's B or C cirrhosis or liver failure are not eligible for standard antiviral therapy and are generally offered liver transplantation and/or supportive care for cirrhosis.

There are no studies from India, which look into clinical spectrum of HCV infection at presentation, with reference to the eligibility for antiviral treatment. Hence, we aimed to study the spectrum of clinical presentation of HCV infection at our center, determined their eligibility for antiviral treatment, and followed those treated for treatment response and their outcomes.

PATIENTS AND METHODS

Patients

This retrospective study was conducted in the Department of Gastroenterology, Sir Ganga Ram Hospital, New Delhi, India. The records of all consecutive patients with HCV disease, above age of 14 years, who presented to our department, between 2008 and 2014, were analyzed. HCV disease was diagnosed when detectable anti-HCV, HCV RNA or both were present in serum. These records were in specific pro-forma for each HCV patient that contained relevant information on clinical presentation, risk factors for HCV acquisition, hematological, biochemical, serological, radiological, and histological investigations. If patient had received antiviral therapy, relevant information to determine treatment outcome had also been recorded in the pro-forma. Those patient-records were excluded from the study that had incomplete data to derive any meaningful conclusion. For missing data on individual parameter, imputation method was employed (8).

Clinical evaluation

These data in pro-forma were analyzed to obtain information on history, physical examination, complete blood count, liver function test, renal function test, prothrombin time, INR, ultrasound abdomen, hepatitis B surface antigen, HIV, ANA, SMA, baseline HCV RNA by quantitative real-time polymerase chain reaction (PCR) assay (Cobas Taqmen 48), HCV genotype by real-time PCR assay and upper gastrointestinal endoscopy, as indicated. Every patient was reviewed for risk factors of HCV acquisition, *viz*. blood transfusion, surgery, needle stick

injury, dental procedure, tattooing, acupuncture, unprotected intercourse with multiple sexual partners and intravenous drug abuse. Patients with significant alcohol intake were defined as those who were consuming regularly >20 g of alcohol per day for at least ten years, prior to presentation.

Clinical Presentation Groups

After complete evaluation the HCV patients were categorized into one of the three presentation groups: Chronic hepatitis, cirrhosis or hepatocellular carcinoma. Diagnosis of cirrhosis was made on the basis of clinical, biochemical, radiologic, endoscopic or histologic findings. Severity of cirrhosis was graded based on the Child-Pugh classification. The diagnostic criteria for HCC were any of the following: hypervascular liver mass on triple-phase contrast-enhanced CT abdomen (with or without raised AFP) or fine needle aspiration cytology (FNAC) (9). Patients with no evidence of cirrhosis or HCC were categorized as chronic hepatitis C. Spontaneously cleared HCV was defined when HCV RNA was not detectable in patients but with positive serology for hepatitis C (Anti HCV).

Eligibility for Antiviral Treatment

All patients who were in stage of chronic hepatitis with detectable HCV RNA were eligible for antiviral therapy. Patients with compensated cirrhosis (Child–Pugh class A) were also eligible for antiviral therapy. Patients who had advanced liver disease in form of Child's B or C cirrhosis or liver failure were not eligible for therapy. Patients on treatment for HCC of BCLC stage A or B were also eligible for antiviral therapy if they had detectable HCV RNA.

All eligible patients were started on a combination therapy of PEG-IFN (α2a or α2b) subcutaneously plus oral ribavirin (RBV) at dosages recommended in the treatment guidelines. Peg-IFN α2a was given at a dose of 180 mcg subcutaneously per week and Peg-IFN α2b was given at a dose of 1.5 mcg/kg subcutaneously per week. Ribavirin was given at a dose of 800 mg/day for genotype 3 patients and at a dose of 1,000 mg for those <75 kg in weight and 1,200 mg for those >75 kg in genotype 1 patients. Information on sustained virological response (SVR), defined as undetectable HCV RNA at 24 weeks after treatment completion, was obtained. Patients whose SVR results were not available due to lost to follow up were considered as failed to have achieved SVR (intention-to-treat analysis).

Statistical analysis

Continuous data was represented as median (range) and categorical data was expressed as number and percentage. Statistical analysis was done using SPSS 17.0 (Chicago, Illinois). To deal with problem of missing data, simple imputation method was employed, in which a single value was filled in for each missing value by means of methods such as the last observation carried forward and the baseline observation carried forward.

RESULTS

Patients

A total of 799 patients of HCV who were admitted during the study period were enrolled. Twenty-two patients were excluded from the study due to incomplete records; hence remaining 777 patients were included in the study and their data was analyzed.

Baseline Characteristics

The baseline characteristics of study patients are shown in Table 1. The median age at presentation was 49 (range 15-95) years and majority of patients were males (69%, 538/777). These patients were known to be HCV positive for a median of 2 months (range 1 to 180 months). Diabetes mellitus was present in 21% (165/777) and 9% (71/777) had ESRD. Nine percent (72/777) patients were obese with a BMI ≥30 kg/m^2. The median BMI of all patients was 24.5 kg/m^2 (range 15.0 to 42.2 kg/m^2). About 19% (149/777) gave history of alcohol abuse in cirrhogenic doses. Co-infection with HIV was present in 0.9% (7/777) patients and with HBV in 1.7% (13/777) patients. Two patients had all the three infections (HCV, HBV and HIV). Past history of surgery was the most common risk factor for HCV acquisition which was present in 35% (274/777) patients; followed by a history of blood transfusion present in 32% (248/777) patients. History of hemodialysis was present in 7% (56/777) and history of dental extraction was present in another 7% (55/777). Other risk factors included needle stick injury in 1.5% (12/777), tattooing in 1% (8/777), IV drug abuse in

1% (6/777), and acupuncture in 0.1% (1/777). Past history of Jaundice was present in 25% (194/777).

Clinical Presentation Groups

After complete evaluation the HCV patients were categorized into one of the three presentation groups: Chronic hepatitis, cirrhosis or hepatocellular carcinoma. Cirrhosis was the most common presentation with 56% (439/777) patients in this group. Chronic hepatitis represented 37% (287/777) patients, while HCC was presented in 7% (51/777) patients. All patients of HCC also had underlying cirrhosis, hence a total of 490 (63%) patients had cirrhosis.

Patients with cirrhosis (including those with HCC) were further categorized into Child-Pugh A, B and C depending on severity. Thirty-six percent (174/490) patients were Child A; 51% (250/490) were Child B and 14% (66/490) had Child C cirrhosis. Ascites was present in 53% (259/490) had ascites and 76% (371/490) had esophageal or gastric varices. Fifteen percent (72/490) cirrhotics had history of variceal bleeding.

Eligibility for Antiviral Treatment

Patients with detectable HCV RNA who have chronic hepatitis or Child A cirrhosis are generally eligible for antiviral treatment with Peg-Interferon and Ribavirin. Of patients with chronic hepatitis in 78% (223/287) had detectable HCV RNA (thus eligible for antiviral treatment), in 8% (22/287) the HCV RNA was negative, and in 15% (42/287) HCV RNA levels were not available. Among

cirrhotic patients, of 174 patients with Child A cirrhosis, detectable HCV RNA was present in 71% (124/174) and were eligible for antiviral treatment. Thus, out of all 777 HCV patients only 347 (45%) were eligible for antiviral treatment. Among the remaining 430 patients in 326 (76%) the disease was far too advanced to offer any antiviral treatment.

Of patients eligible for antiviral treatment only 54% (189/347) actually received antiviral treatment. The rest could not receive treatment mainly because it was unaffordable for them. Moreover, eighty-one percent (153/189) patients could complete the antiviral treatment and of them 70% (107/153) could achieve the sustained virological response (Figure 1).

DISCUSSION

This is the first study from India, which clearly documents that majority of patients of HCV in India, at their clinical presentation have advanced disease, and they have already lost their chance of complete cure of their HCV related liver disease. The only hope for these patients with advanced HCVrelated liver disease is liver transplantation. Our study showed that of 777 consecutive patients of HCV who presented to our department from 2008 through 2014, only 45% were eligible for antiviral treatment with Peg-interferon and Ribavirin. Cirrhosis was already present in 63% patients, and it was advanced (Child B or C) in 65%. HCC was presented in 7%.

HCV has a huge disease burden in India (1). The data on prevalence of HCV infection in India is scanty and the only sources are a few screening studies done on blood donors and pregnant women, and few community-based studies. In India, mandatory screening for HCV started in 2000 (6). The seroprevalence of anti-HCV in blood donors in various places in India, since the year 2000, has ranged from 0.13 to 1.09% (10–15). Seropositivity of HCV in antenatal women in India ranges from 0.19% to 1.6% (16,17). These data, however, cannot be extrapolated to the community as blood donors and pregnant women represent a selected and healthy population sample. In a community-based epidemiologic study, which was carried out in a district in West Bengal, of 3579 individuals screened, 0.87% were HCV antibody positive (18). As compared to West Bengal, in states of Punjab and Haryana the prevalence of HCV seems to be much higher. In a study done by Sood et al. (19), prevalence rate of HCV infection in Mullanpur (district Ludhiana of Punjab) was found to be 5.2% of 5258 subjects screened

door-to-door. This prevalence rate is possibly the highest in South Asia. Data from rest of the country are very limited. Data from western India revealed a seroprevalence of 0.78 % (20). Thus an estimated average prevalence of 0.8% (0.4%-1.0%) is reasonably suggested by a recent meta-analysis (21). Although the prevalence of HCV infection in Indian population is lower than that reported from industrialized countries of the west, the total reservoir of infection is significant. The WHO estimates that approximately 12 million Indians are suffering from HCV (while the prevalence in the US is just 2-4 million and in Europe is 5-10 million) (22). This calls for urgent public health measures, including health education to limit the magnitude of the problem (18).

In our study we showed that by the time patients of HCV present to hospitals, 63% already have cirrhosis. The reason for this late presentation is that most HCV patients in the early stage (chronic hepatitis stage) either have no symptoms or have only very mild non-specific symptoms. In a community study from Haryana on 1630 cases of HCV (23), only fatigue was the most common symptom present in 69% of patients, followed by abdominal pain in 47%. Symptoms like malaise and body ache were found among 14% of patients in this study (23). In community, till very late stage of disease, these non-specific symptoms are treated symptomatically, and blood tests are usually not carried out. Even if biochemical investigations are done, they are usually normal. In the community study from West Bengal, serum alanine aminotransferase (ALT) levels were elevated in only 31% (8 of 26) of anti-HCV-positive subjects (18). In spite of mild or no symptoms and normal or near normal biochemistry, these patients are infective, even though they do not know they are infected, and have a potential to spread the disease to others. These asymptomatic individuals

comprise of a large reservoir of HCV carriers, who can act as a pool for its continuous transmission (24). HCV RNA is detectable in more than 80% of these cases suggesting actively replicative virus with potential of transmission (18). As no protective vaccine is available and as the treatment is costly, lengthy, with a poor success rate, screening of healthy population remains the only means of primary prevention of HCV transmission (10). Routine blood screening for Hepatitis C infection should be mandatorily carried out in all hospitals.

The only method to control the HCV pandemic is prevention of HCV transmission and early treatment of those infected. Over the last few years, numerous HCV vaccine approaches have been assessed in mice and primates, but only a few vaccines have progressed to human trials (25). Since, there is no hepatitis C vaccine available as yet, the only other preventive method is safe healthcare practices. Unsafe therapeutic injections and transfusion of unsafe blood are the predominant mode of transmission of HCV in India (1). Unsafe therapeutic injections include contaminated multi dose vials and saline bags from reinsertions of used needles and syringes, use of single needle or syringe to administer intravenous medication to multiple patients, and also due to the use of spring loaded finger stick devices without changing the platform to monitor blood sugar levels in multiples patients (26,27). Hence, to reduce the burden of HCV infection and to decrease the incidence of HCV infection, health care workers should play an important role (28). The safe injection practices should be followed meticulously. These include the use of aseptic technique for injection equipment, not to administer medication from same syringe to multiple patients, use of fluid infusion and administration sets for one patient only, use of single

dose vials, not to administer medication from single dose vial to multiple patients or combine leftover contents (26).

The natural history of HCV shows that the majority of patients may become chronically infected and will not spontaneously resolve the infection. About 20% of chronically infected patients will evolve to cirrhosis within 25–30 years, with an increased risk of hepatic decompensation and HCC. The goal of HCV treatment is to eradicate the virus and prevent the complications of chronic liver disease. The standard-of-care for HCV, till recently, has been combination therapy with Peg-IFNα/RBV (29). Although in the latest guidelines from AASLD and EASL in 2014 have already incorporated DAAs in the management of patients with HCV. The newly approved DAA are yet to reach the Indian market. Selecting patients for antiviral therapy with Peg-IFNα/RBV is mainly based on patient factors including fibrosis stage, probability of adverse events of therapy, and comorbidities, such as chronic kidney disease or psychiatric disease, that may preclude or modify therapy options. Decompensated chronic liver disease is an absolute contraindication for therapy. Thus only a proportion of HCV patients are eligible for antiviral therapy, and our study has showed that in India, most patients are already ineligible by the time they present.

Attaining SVR (sustained viral response) has been associated with decreases in all-cause mortality, liver-related death, need for liver transplantation, HCC, and liver-related complications. In our study, of those patients who could complete the treatment with Peg-IFNα/RBV, 70% were able to achieve SVR. Based on the genotype profile of HCV in India (genotype 3 68% and genotype 1 26%) a SVR of 70% is reasonable and compares well with data

from West. However, the alarming fact is that even if the patient was a good candidate for antiviral therapy, it could be started in 54% patients and only 81% could complete the therapy. Thus out 347 patients who were eligible for antiviral therapy only 44% (153/347) could actually receive and complete the therapy The main reason for this dismal data with treatment obtainment and compliance is poor economic condition of the patients. According to the data from the Reserve Bank of India in 2012, the population India living below poverty line was 21.92% (30). Most Indian patients have no medical insurance to cover the cost of therapy.

Recent years have seen development of a large number of new molecules that are revolutionizing the treatment of hepatitis C. Some of the new directly acting agents (DAAs) like sofosbuvir have been called game-changers because they offer the prospect of interferon-free regimens for the treatment of HCV infection (29). Sofosbuvir is a highly potent inhibitor of the NS5B polymerase in the HCV, and has shown high efficacy in combination with several other drugs, with and without PEG-INF, against HCV (31). It offers many advantages due to its high potency, low side effects, oral administration, and high barrier to resistance. The efficacy and safety were demonstrated in many large and well-designed phase 2 and phase 3 clinical trials like NEUTRINO (32), PROTON (33), ELECTRON (34), ATOMIC (35), COSMOS (36), FUSION (37), FISSION (32), NUCLEAR (38), POSITRON (37), and the like. It is generally well-tolerated. Adverse events that occurred include: Headache, insomnia, fatigue, nausea, dizziness, pruritis, upper respiratory tract infections, rash, back pain, grade 1 anemia, and grade 4 lymphopenia; however, the exact safety profile can only be judged when this drug is actually used on a large scale (31).

However, these new DAAs have not yet been approved in India and their cost and availability is uncertain at present. Till these drugs become available at an affordable cost, the treatment that was standard of care for the whole world before these newer drugs were approved should continue to be recommended in India. It may be prudent to withhold treatment at present for selected patients with genotype 1 or 4 infection and low levels of fibrosis (F1 or F2), and for patients who are non-responders to initial therapy, interferon intolerant, those with decompensated liver disease, and patients in special populations such as stable patients after liver and kidney transplantation, HIV co-infected patients and those with cirrhosis of liver. However, in patients with advanced fibrosis (fibrosis score F3 or F4), compensated cirrhosis or significant extrahepatic manifestations (symptomatic cryoglobulinemia or HCV immune complexes nephropathy) or in those likely to have good response to IFNα/RBV (eg. genotype 3 CH–C), it may not be advisable to wait and treatment should be started (29).

Thus to conclude, most patients of HCV infection in India present late and only about 45% are eligible for antiviral treatment with Peg-interferon and Ribavirin. At presentation 56% patients already have cirrhosis and 7% have HCC. Since HCV is usually asymptomatic at treatable stage, awareness about screening should be increased so that more patients are diagnosed at treatable stage.

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TABLES

Table 1: Baseline characteristics of included patients.

Parameter	Value	
Age, years	49	(15 – 95)
Gender, % (n/n)		
Males	69%	(538/777)
Females	31%	(239/777)
BMI, kg/m^2	24.5	(15.0 – 42.2)
Known to be HCV+ for, months	2	(1 – 180)
Co-morbities, % (n/n)		
Diabetes	21%	(165/777)
Alcoholics	19%	(149/777)
ESRD	9%	(71/777)
Co-infections, % (n/n)		
HIV	0.9%	(7/777)
HBV	1.7%	(13/777)
	(two patients had all the three infections: HCV, HBV, HIV)	
Risk factors for HCV acquisition, % (n/n)		
Blood transfusion	32%	(248/777)
Dental extraction	7%	(55/777)
Surgery	35%	(274/777)
Needle stick injury	1.5%	(12/777)
Tattoo	1%	(8/777)
Acupuncture	0.1%	(1/777)
Dialysis	7%	(56/777)
IV drug abuse	1%	(6/777)
Past history of jaundice, % (n/n)	25%	(194/777)
HCV RNA, % (n/n)		
High (>4×10^5 IU/mL)	45%	(261/581)
Low (615 to 4×10^5 IU/mL)	46%	(269/581)
Undetectable or very low (<615 IU/mL)	9%	(51/581)
HCV genotype, % (n/n)		
Genotype 3	68%	(319/470)
Genotype 1	26%	(121/470)
Genotype 4	4%	(18/470)
Genotype 2	1%	(6/470)
Genotype 3+4	1%	(4/470)
Genotype 1+3	0.5%	(2/470)
IL28b, % (n/n)		
C/C	53%	(61/115)
C/T	42%	(48/115)
T/T	5%	(6/115)

FIGURES

Figure 1: HCV disease pyramid with respect to treatment eligibility and treatment success rate.