The clinical features and treatment outcome of chronic hepatitis C with pegylated interferon and ribavirin in routine care

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ABSTRACT

Aim: To describe the clinical characteristic of hepatitis C (HCV) patients and the results of pegylated interferon and ribavirin (PegIFN/RBV) therapy in a routine clinical practice.

Methods: A retrospective review of consecutive HCV patients treated with PegIFN/RBV in 2004 to 2012.

Results: A total of 273 patients received treatment. The mean age was 44.16 ± 10.5 years and 76% were male. The top 2 self-reported risks were blood or blood product transfusion before 1994 and injection drug use, found in 57.1% of patients. The predominant HCV genotype (GT) was 3 at 60.6%, second was GT1 at 36.1% and other GTs were uncommon at about 1% or less. About half of our patients have high baseline viral load (>800,000 iu/ml), 18.3% had liver cirrhosis and 22.3% had HIV co-infection. Co-morbid illness was found in 42.9%, hypertension and type 2 diabetes were the two most common. The overall sustained virological response (SVR) by intention-to-treat analysis were 54.9% (n=150/273), 41.2% (40/97) for GT1, 100% (5/5) for GT2 and 62% (101/163) for GT3. Subgroup analysis for HCV monoinfected, treatment naïve showed SVR of 49.2% (31/63) for GT1, 100% (5/5) for GT2 and 67% (69/103) for GT3. In HCV mono-infected and treatment experienced (n=29), the SVR was 28.6% (4/14) for GT1, 21.4% (69/103) for GT3. In the HIV/HCV co-infected, treatment naïve (n=56), the SVR was 28.6% (4/14) for GT1 and 64.3% (27/42) for GT3. Treatment naïve GT3 mono-infected patients had a statistically significant higher SVR compared to treatment experienced patients (P=0.001). In GT3 patients who achieved rapid virological response, the SVR was significantly higher at 85.2% (P< 0.001). The SVR for cirrhotics were low especially for GT1 at 21% (4/19) and 31% (4/13) based on all patients and treatment naïve HCV monoinfected respectively. In GT3 cirrhotics the corresponding SVR were 57.1% (16/28) and 60.9% (14/23). Premature discontinuation rate was 21.2% with the majority due to intolerable adverse events at 12.1%.

Conclusions: In our routine clinical practice, the HCV patients we treated were young, predominantly of GT3 and many had difficult-to-treat clinical characteristics. The SVR of our patients were below those reported in Asian clinical trials but in keeping with some "real world" data.

KEY WORDS:
Hepatitis C; "real world"; pegylated interferon and ribavirin; sustained virological response; adverse events

INTRODUCTION

The World Health Organization estimated there are 130-150 million people living with hepatitis C virus (HCV) worldwide and certain parts of Asia are amongst the regions with high to moderate prevalence rates.[1,2] HCV is one of the leading causes of chronic liver disease, cirrhosis and hepatocellular carcinoma globally with approximately 500,000 people succumbed to HCV related liver disease annually.[1]

In Malaysia, it had been estimated that 454,000 individuals were sero-positive for HCV in the year 2009.[3] According to the report, this represents 2.5% of the population aged between 15–64 years. Similarly another group of researchers estimated the prevalence of hepatitis C in the country to be at 2%.[2] The Global Burden of Disease study 2010 estimated that slightly over 1300 deaths were attributed to hepatitis C infection in Malaysia for the year 1990-2010.[4] In a local study from a university hospital, HCV was found to account for 18.5% of all cirrhotic patients seen in the period between 2006 and 2009.[5] Based on the reports in health facts documents published by the Ministry of Health, Malaysia, from the year 2009 to 2015 there are an increasing number of HCV cases that had been notified.[6] The reported cases are likely an underestimate of the true picture due to various factors as well as the difficulty in diagnosing acute HCV which is usually asymptomatic or has non-specific symptoms.[7] For these reasons, HCV is of public health concern and the burden of disease from HCV infection is expected to increase as the infected population ages.

The goal of HCV therapy is attaining sustained virological response (SVR). Achieving SVR in HCV patients has been shown to decrease not only liver-related but also all-cause mortalities. SVR also reduces the risks of liver failure, hepatocellular carcinoma and the need for liver transplant.[8] If SVR was attained after the development of liver cirrhosis, there are still benefits from decrease in liver-related morbidity and mortality and the need for liver transplant, however the risk for hepatocellular carcinoma remains.[9] It is reassuring from a prospective study that the SVR from pegylated

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interferon with or without ribavirin was found to be durable in 99.1% of a large cohort of patients followed up over a mean of 3.9 years.[10]

There are major rapid advances in the treatment of chronic HCV infection in the last few years with the advent of multiple drugs called the direct acting antiviral (DAA). In contrast to pegylated interferon and ribavirin (PegIFN/RBV) treatment, the short duration of treatment with oral DAAs medications causes only minimal to mild side-effects yet achieving high SVR rates at 90% and above.[1] However these newer therapies are currently out of reach for most patients with HCV in the country due to the high cost and resource constraints in our health systems which are mainly provided by the government.[6,11] Dual therapy with pegylated interferon and ribavirin (PegIFN/RBV) which are provided by the government is still the mainstay of anti-HCV therapy in our country.

Similar to some countries in South and South East Asia, the predominant HCV in Malaysia is HCV genotype 3 at 61.9% and the second common genotype is 1 at 35.9% with very few at 1% or less for the other genotypes.[12] Unfortunately HCV genotype 3 is associated with more severe liver disease as well as less impressive response to the currently approved DAAs compared to other HCV genotypes.[13] Genotype 3 was also found to be an independent risk factor for fibrosis progression[14] and hepatocellular carcinoma.[15] Moreover the treatment of HCV genotype 3 with PegIFN/RBV has been reported to result in lower SVR rates compared to genotype 2.[16]

A review of clinical trials on PegIFN/RBV therapy for HCV in Asia had reported high response rates at about 85 to 90% for HCV genotype 2 or 3 and 70% to 75% for genotype 1 or 4.[17,18]

Gaps between "real world" data from routine clinical practice and data from clinical trials are to be expected, these arise from different selections of patients who are bound to be sicker with more advanced liver diseases and co-morbidities and different treatment setting in our day to day clinical practice. However results from routine clinical practice may provide more useful informations for clinicians and also the policy makers.

The aim of this study is to collate the baseline clinical features of HCV infected patients who were assessed for PegIFN/RBV treatment and analyze the sustained virological response in our routine clinical practice. We would like to find out if PegIFN/RBV still has a role in selected group of patients and secondly to be better informed on who to prioritize for the costly yet more effective newer DAA therapies.

MATERIALS AND METHODS

Recruitment of participants

We conducted a retrospective review of the electronic medical records from a database of HCV patients treated by the Hepatology Department of Selayang Hospital which is a hospital in the public sector. All patients who were prescribed dual therapy with Pegylated Interferon (PegIFN) alfa 2a or 2b plus Ribavirin (RBV) between the year 2004 to 2012 for the diagnoses of chronic hepatitis C were included. These patients were referred by primary and secondary care services of both public as well as private sectors from the central region and various states in the country.

Assessment and evaluation

The patients were seen in the Hepatology Clinics, at the first clinic visits thorough clinical examinations were carried out by the attending hepatologists /gastroenterologists /trainees Hepatitis counselling and educations were also provided at a one-to-one basis by trained nurses. If indicated some patients were referred for psychiatric evaluation. The investigations consist of blood counts, liver function tests, renal profile, thyroid function tests, antinuclear antibody, HBsAg, antiHIV, anti-HCV antibody, liver ultrasound, HCV RNA[Quantitative analysis: CobasAmplicor Monitor Test V2.0 (Roche, Branchburg, NJ USA); range 600-700,000 IU/ml. After March 2006: Cobas Ampli Prep/Taqman (Roche, Branchburg, NJ USA); range 43-69,000,000 IU/ml] and HCV genotype [INNO-LIPA HCV 2.0 (Innogenetics NV, Ghents, Belgium). After 2008: Siemens Versant HCV Genotype assay (LiPA 2.0)]. Patients with abnormal thyroid function tests or antinuclear antibody greater than 1 in 320 are investigated further to rule out any contraindication to interferon therapy.

The severity of liver disease was assessed by liver biopsy before October 2010 except in cases with existing clinical, laboratory and imaging evidence of liver cirrhosis or patients' refusal especially if the HCV genotypes were 2 or 3. Fibrosis (F) was staged by Modified Histology Activity Index System with the following score: {F0=no fibrosis, F1=fibrous expansion of some portal tracts ± short fibrous septa, F2=fibrous expansion of most portal tracts ± short fibrous septa, F3=fibrous expansion of most portal areas with occasional portal to portal bridging, F4=fibrous expansion of most portal areas with marked bridging portal to portal as well as portal-central, F5=marked bridging (portal-portal and/or portal-central) with occasional nodules, F6=cirrhosis}. Thereafter liver fibrosis was assessed by transient elastography (FibroScan; Echosens, Paris, France). We convert the liver stiffness measurements by transient elastography to Metavir fibrosis stage using the cut-off values of 7.1 kPa for Metavir F≥2, 9.5 kPa for Metavir F≥3, and 12.5 kPa for Metavir F=4. [19] The Metavir fibrosis was staged as follows: F0=no fibrosis; F1=portal fibrosis without septa; F2=portal fibrosis and few septa; F3=numerous septa without cirrhosis and F4= cirrhosis.

Significant fibrosis is defined as modified HAI fibrosis scores ≥ F3 or Metavir scores ≥ F2. Liver cirrhosis is defined as Modified HAI Fibrosis stage 6, valid liver stiffness measurements > 12.5 KPa by transient elastography or platelet counts less than 150,000 and irregular liver margin on imaging or other evidence of portal hypertension on endoscopy and imaging.

Treatment and routine care

The treatment regimen consisted of PegIFNalfa 2a at 180µg or 2b at 1.5µg/kg weekly subcutaneous injection plus oral RBV with the following dose: for genotype 2 and 3 at 800mg daily and in later part of the study period we used 15 mcg/kg/day for obese patients and for genotype 1 and 4 at 1000mg daily when bodyweight of 75kg and below or at

1200mg daily when the bodyweight was more than 75kg. In haemodialysis patients we used reduced doses of both PegIFN and RBV which were PegIFN alfa 2a at 135 µg or 2b at 1.0 µg/kg weekly and oral RBV at 200 to 400 mg daily.

Mono-infected, treatment naïve HCV patients with genotype 1, 4 and 6 received 48 weeks of PegIFN/RBV treatment while genotype 2 and 3 patients were given 24 weeks. In the later part of the study, those who achieved rapid virological response (RVR) defined as undetectable HCVRNA at week 4 of PegIFN/RBV and have other good prognostic markers like non diabetics, treatment naïve, baseline viral load less than 800,000 iu/ml, HCV monoinfection and absence of liver cirrhosis were given shorter durations of treatment 24 weeks for genotype 1 and 16 weeks for genotype 3. Treatment-experienced patients were treated with extended duration of treatment, 48 weeks for genotype 2 and 3 and 72 weeks for genotype 1. HIV/HCV co-infected patients were treated for 48 weeks regardless of genotype. Genotype 1 patients who had less than 2 log10iu/ml decreases in HCV RNA titre at week 12 of PegIFN/RBV treatment compared to the baseline viral load were considered as having null response and their treatment were stopped. Later in the study period, genotype 3 HIV/HCV co-infected patients, with low baseline HCV RNA, minimal liver fibrosis and RVR were treated for 24 weeks especially if they experienced troublesome adverse effects (AE).

The treatment was initiated as in-patient; the patients were given educations and advice on anticipated side effects and suggestions on how to ameliorate them. Patients were also taught how to prepare the injections, drug administration and other self-care. During treatment, the patients were followed up by the same clinician throughout the treatment period at 2 weeks and 4 weekly thereafter with blood counts and liver function tests. More frequent follow-up was performed on complicated cases at the attending clinicians' discretions. Thyroid function tests were carried out 3 monthly. Anemia was managed by RBV dose reduction and blood transfusion if necessary. Modifications of the doses of PegIFN/RBV are mostly according to product inserts with some variations reflecting the clinical practice of the attending clinicians.

In the later 2 years from 2010 onwards, the patients were also co-managed with our pharmacists in the medications therapy adherence clinics (MTAC). This dedicated pharmacist assisted in ensuring treatment adherence, proper injection techniques and medication storage.

Assessment of Response and Safety

The response to treatment was assessed at the end of treatment (ETR) and 24 weeks after the completion of treatment for sustained virological response (SVR). Both are defined as undetectable HCV RNA [(<50 IU/ml by qualitative PCR; CobasAmplicor Monitor Test V2.0 (Roche, Branchburg, NJ USA0] at their respective time points. Safety was assessed by clinical evaluation for AE during therapy and laboratory tests.

Statistical analysis

All analysis was performed using SPSS® software application version 20.0 for Windows® (SPSS IBM New York, USA). The clinical profile of chronic hepatitis C patients treated in Selayang Hospital was determined by means with standard deviation (SD) or median and interquartile range (IQR 25% & 75%) for continuous data and frequency (%) for categorical data. Patients who received at least one dose of PegIFN/RBV were included into an intention–to-treat analysis for efficacy and safety. Chi-square or Fisher's exact test was used to compare categorical variables. To assess the independent factor related to SVR, a multivariate analysis was performed using enter-method logistic regression. All tests were two sided and $p<0.05$ was considered to be statistically significant.

Ethical considerations

This study received approval from the Medical Research and Ethics Committee and is registered in the National Medical Research Register NMRR-14-1156-22102.

RESULTS

Baseline Characteristics

A total of 273 HCV patients were treated in our institution from the year 2004 to 2012. The baseline characteristics of the study population are listed in (Table I). At the time of treatment initiation, the age ranges from 14- 68 years old with a mean age of 44.16 ± 10.5 years. The predominant gender was male at 76.6% and 53.4 % of our patients had BMI > 23 kg/m^2.

The majority of our patients (88.3%) was treatment naïve, while 11.7% were treatment experienced with previous exposure to either pegylated interferon and ribavirin regimen (n=17) or standard interferon and ribavirin regimen (n=14) or pegylated interferon alone (n=1).

Pre-treatment, forty one patients (15.1%) had normal alanine transaminase (ALT) levels however the majority (80.1%) had elevated baseline ALTs at levels between one to five times upper limit of normal.

One hundred and seventy five patients agreed for liver biopsy, the state of fibrosis were assessed by Modified Histology Activity Index System (Modified HAI). After October 2010, we assessed liver fibrosis by transient elastography using Fibroscan® and their results are reported in (Table I). A total of 49 patients (18.3%) were found to have liver cirrhosis pre-treatment. Another 32.9% were found to have significant fibrosis. A large number of our HCV patients (42.9%) have other co-morbid illness, the two most common ones were hypertension at 17.6 % and 11.4 % have type 2 diabetes.

Hepatitis C virus genotype were available in 269 patients and it was predominantly genotype 3 (n=163, 60.6%) followed by genotype 1 (n=97, 36.1%). The remaining few cases were of genotype 2 (n=5, 1.8%) genotype 4 (n=3, 1.1%) and genotype 6 (n=1, 0.4%) infections. Slightly more than half of our patients (50.8 %) had high baseline viral load HCV RNA at > 800,000 IU/ml. Co-infection with other blood borne viruses were found in 56 patients with HIV and HCV, in eight patients with hepatitis B (HBV) and HCV and five patients with triple infections with HIV, HCV and HBV.

The top 2 common modes of transmission according to patients' self-report were blood or blood product transfusion before 1994; the year hepatitis C screening started in blood donors (28.2%) and injection drug use (28.9%). The former was more common in females whilst the latter was mainly reported by male patients. However, a number of patients (17.6%) denied having any of the frequently reported risk factors while 15.4% reported multiple factors. Results are summarized in (Table II).

Treatment Details

In our centre during this study period, 69.6% (n=190/273) were treated with pegylated interferon alfa-2a and the remaining 30.4% (n=83/273) with pegylated interferon alpha-2b.

Premature discontinution of treatment occured in 62 patients (22.7%) treated in our center. Thirty three patients (12.1%) were unable to complete treatment due to adverse events, 5.5% (n=15) defaulted treatment and follow-up while fourteen patients (5.1%) had early treatment discontinuation due to null response to PEG/RBV. See Figure 1.

During treatment, 72 (26.4%) patients required PegIFN dose reduction and 76 (27.8%) required RBV dose reduction. PegIFN dose reduction affects the efficacy of treatment (p = 0.012) while dose reduction of RBV did not (p = 0.223).

Safety and adverse events

One or more adverse events (AE) were reported in 246 patients (90.1%). The most common AEs patients complained about were myalgia, arthralgia, general lethargy and fatigue (n=136, 23%). Generally patients were able to tolerate these AE with only one patient who requested to discontinue treatment due to severe fatigue.

The second common AE reported by our patients is neuropsychiatric disorder (n=97, 17%). Suicidal ideation, irritability, unexplained mood swings, depression and lowered threshold of anger were among the symptoms. Five patients' required specific additional medications to control these symptoms and their PegIFN/RBV therapies were successfully completed. One patient was diagnosed with schizophrenia with hallucination at three months after achieving SVR and had to be warded. It was unclear if the treatment contributed to the event.

Another common AE was dermatological, 15% (n=88) the complaints were dry skin, rashes, alopecia, dermatitis and pruritus. These symptoms were easily controlled by mainly topical medications.

Twelve percent (n=71) AEs were due to laboratory haematologic abnormalities, 18 patients (6.6%) had to be transfused with a total of 91 pints of blood during their treatment period. We did not use haemopoetic growth factors for our patients. In twenty patients (7.3%), PegIFN/RBV treatment was discontinued due to severe anaemia (the lowest hemoglobin=7g/dL), thrombocytopenia (the lowest platelet counts=18,000) or neutropenia (the lowest absolute neutrophil count=0.3 x 109/L) despite after adjusting the doses of PegIFN/RBV.

A single case of symptomatic hepatitis with ALTs above twice the baseline level reaching almost 10 times upper limit of normal with mild increase in serum bilirubin was recorded. His treatment was discontinued immediately and he recovered with attainment of SVR. The other adverse drug events recorded involved the respiratory system (coughing), central nervous system (dizziness, giddiness, headaches), cardiovascular system (palpitation, chest pain), ophthalmology (blurring of vision), metabolism and nutrition related (loss of appetite & weight, dysgeusia and nausea) and mild infection.

The total number of patients who discontinued treatment due to intolerable AE was 33 (12.1%) and there was no documented mortality.

Response to Treatment

Results for HCVRNA were missing in 12 patients for end of treatment response (ETR) and in 15 patients for sustained virological response (SVR). These missing data were considered non responders in the intention-to-treat (ITT) analyses. The overall ETR was 71.4% (n=195/273). Four patients did not have HCV genotype results, hence the ETR according to HCV genotypes were 58.8% (n=57/97) for genotype 1, 100% (n=5/5) for genotype 2, 78% (n=127/163) for genotype 3, 66.7% (n=2/3) for genotype 4 and 100% (n=1/1) for genotype 6. All of the five genotype 2 patients treated achieved ETR while genotype 3 showed a significantly higher ETR rate compared to genotype 1 (78% versus 58.8%, p= 0.01). See (Table III).

Taking as a group of all the HCV patients treated and based on ITT analyses, the overall SVR rate was 54.9% (n=150/273). The SVR were 41.2 % (40/97) for genotype 1, 100 % (5/5) for genotype 2 and 62 % (101/163) for genotype 3 (p<0.001). None of the three genotype 4 patients and the one genotype 6 patients achieved SVR.

Subgroup analyses of SVR based on HCV mono-infection patients only and according to HCV genotypes plus previous treatment status showed, in HCV monoinfected, treatment naïve patients who had genotype data(n=174), the SVR was 49.2%(31/63) for genotype 1, 100% (5/5) for genotype 2 and 67% (69/103) for genotype 3. HCV mono-infection and treatment experienced (n=29), the SVR was 28.6% (4/14) for genotype 1, 21.4% (3/14) for genotype 3 and the one genotype 4 who were re-treated did not achieve SVR. Results on subgroup analyses are summarized in (Table IV).

Similar subgroup analyses in the HIV/HCV co-infected patients showed for treatment naïve (n=56), the SVR was 28.6% (4/14) for genotype 1 and 64.3% (27/42) for genotype 3. There were only 2 treatment experienced HIV/HCV co-infected patients who were re-treated and both did not achieve SVR. Results are summarized in (Table IV).

In the cirrhotic patients (n=49), the overall SVR was 44.9% (22/49), the SVR for genotype 1 was 21% (4/19), for genotype 2 was 100% (2/2) and for genotype 3 was 57.1% (16/28). None of the genotype 4/6 patients were cirrhotic. In the HCV mono-infected cirrhotic and treatment naïve patients (n=38), the SVR was 31% (4/13) for genotype 1, 60.9% (14/23) for

Table I: Baseline characteristics of patients (N=273)

Variables	Overall (n = 273)
Age in years	
Mean ± SD	44.16 ±10.51
Gender, Male, n (%)	209 (76.6)
Body mass index (n = 204)	
Underweight (<18.5 kg/m^2), n (%)	17 (8.3)
Normal (18.5-<23 kg/m^2), n (%)	78 (38.2)
Overweight (≥23-<27.5 kg/m^2), n (%)	72 (35.3)
Obese (≥27.5 kg/m^2), n (%)	37 (18.1)
Treatment Status	
Naïve, n (%)	241 (88.3)
Experienced , n (%)	32 (11.7)
• PegIFN +RBV	17
• PegIFN monotherapy	1
• Standard IFN +RBV	14
ALT (u/l) (n=271)	
Mean ± SD	90.9 ± 54.5
Normal, n(%)	41 (15.1)
>1 – 2xULN,n(%)	104 (38.4)
>2xULN-5xULN,n(%)	113 (41.7)
>5xULN,n(%)	13 (4.8)
Hemoglobin (g/dL) Mean ± SD	14.4 ± 1.5
Platelet (x 10^3 µL) Mean ± SD	179 ± 60
White Blood Count (x 10^3 µL) Mean ± SD	6.56 ± 2.1
Absolute Neutrophil Count (x 10^3 µL) Mean ± SD	3.4 ± 1.4
Liver cirrhosis, (n=268), n(%)	49 (18.3%)
Liver Fibrosis Score	
By Liver Biopsy and Modified HAI score (n=175)	
F0, n (%)	6 (3.4)
F1, n (%)	44 (25.1)
F2, n (%)	33 (18.9)
F3, n (%)	41 (23.4)
F4, n (%)	19 (10.9)
F5, n (%)	19 (10.9)
F6, n (%)	13 (7.4)
By Transient Elastography and Metavir Score (n=45)	
F0/F1 (<7.1kPa)	11 (24.4)
F2 (7.1-9.4 kPa)	4 (8.9)
F3 (9.5-12.4 kPa)	5 (11.1)
F4 (≥ 12.5 kPa)	25 (55.6)
Pre-existing Co-morbidities	
None, n (%)	156 (57.1)
Type 2 Diabetes Mellitus, n (%)	31 (11.4)
Hypertension, n (%)	48 (17.6)
Kidney Disorder, n (%)	15 (5.5)
Blood Related Disorder, n (%)	19 (7.0)
Other Heart Related Disorder, n (%)	4 (1.5)
HCV RNA ((iu/ml), (n=264)	
Median (range)	838,000 (2,390-22,500,000)
IQR	229,700; 3,380,000
≤ 800,000 iu/ml, n(%)	130 (49.2)
> 800,000 iu/ml, n(%)	134 (50.8)

Variables	Overall (n = 273)
HCV Genotype(n = 269)	
Genotype 1, n (%)	97 (36.1)
1a, n (%)	55 (20.4)
1b, n (%)	35 (13.0)
1a/1b, n (%)	7 (2.6)
Genotype 2, n (%)	5 (1.8)
2a, n (%)	3 (1.1)
2b, n (%)	2 (0.7)
Genotype 3, n (%)	163 (60.6)
3a, n (%)	161 (59.9)
3b, n (%)	2 (0.7)
Genotype 4, n (%)	3 (1.1)
Genotype 6a, n (%)	1 (0.4)
Co-infection Status	
HIV	56
HBV	8
HIV and HBV	5

SD=standard deviation; PegIFN +RBV =pegylated interferon and ribavirin; Standard IFN +RBV=standard interferon and ribavirin; ALT= alanine transaminase; ULN=upper limit of normal (laboratory upper limit of normal for ALT male=43 u/l, for female=33 u/l); Modified HAI score =Modified Histological Activity Index; HCV=hepatitis C virus; IQR=interquartile range; HIV=human immunodeficiency virus; HBV=hepatitis B virus.

Table II: Presumed risk factors for HCV infection as reported by the patients

Self Reported Risk Factors	n (%)	Male n (%)	Female n (%)
Injection drug use	79 (28.9)	77 (97.5)	2 (2.5)
Blood and Blood Product Transfusion before 1994	77 (28.2)	34 (44.2)	43 (55.8)
Heterosexual Encounters	17 (6.2)	15 (88.2)	2 (11.8)
Tattoo	3 (1.1)	3 (100)	0 (0)
Homosexual Encounters	3 (1.1)	3 (100)	0 (0)
Needle Stick Injury	3 (1.1)	2 (66.7)	1 (33.3)
Hemodialysis	1 (0.4)	1 (100)	0 (0)
Multiple Factors	42 (15.4)	42 (100)	0 (0)

Note: Multiple factors includes two or more of the factors listed in the table

Table III: The overall ETR and SVR of all patients (n=273) and according to HCV genotype.

	Overall (n=273)	Genotype 1 (n= 97)	Genotype 2 (n=5)	Genotype 3 (n= 163)	Genotype 4 (n=3)	Genotype 6 (n=1)	P value
ETR	196/273 (71.8%)	57/97 (58.8%)	5/5 (100%)	127/163 (78%)	2/3 (66.7%)	1/1 (100%)	0.006
SVR	150/273 (54.9%)	40/97 (41.2%)	5/5 (100%)	101/163 (62%)	0/3 (0%)	0/1 (0%)	<0.001

Note: 4 patients did not have HCV genotype done and were excluded in the analysis according to genotype.
ETR=end of treatment response, SVR=sustained virological response

genotype 3 and 100% for genotype 2 (2/2). The two treatment experienced cirrhotic patients who were genotype 1 did not achieved SVR. In the HIV/HCV co-infection cirrhotic patients, all were treatment naive (n=9), the SVR was 40% (2/5) for genotype 3 while all the four genotype 1 patients did not achieve SVR.

In the small number of patients with HBV/HCV co-infection (n=8), the SVR rate was 37.5%.

Rapid virological response (RVR) was assessed only in 90 patients when its use as a predictor of response was evident later, of these 42.2% achieved RVR. The rates of RVR were highest in genotype 3 patients at 50% (27/54), in genotype 1 it was 26.5% (9/34). Irrespective of HCV genotype, the SVR rates in those who achieved RVR was significantly higher compared to those without RVR (81.9% versus 28.8% ; odds ratio (OR) 10.924; 95% confidence interval (CI) 3.954 to 30.178; p<0.001). In genotype 3 patients who achieved RVR (n=27), the SVR rate was 85.2% (23/27) (p< 0.001).

We analysed the baseline and on-treatment characteristics for predictors of SVR. Baseline platelet counts, treatment naïve, low viral load (< 800,000 iu/ml), EVR and RVR were statistically significant on univariate analysis. However on multivariate logistic analysis, only RVR (OR 10.870; 95% CI 3.866-30.564; p<0.001) was significantly associated with SVR.

Table IV : Virological Response according to HCV genotypes, treatment status and HCV mono-infection versus HIV/HCV+HBV co-infection. (n=261)

Variables	HCV mono-infected (n= 203)		HIV/HCV co-infected (n=53) HIV/HCV/HBV co-infected (n=5)	
	Treatment Naïve (n= 174)	Treatment Experienced (n= 29)	Treatment Naïve (n= 56)	Treatment Experienced (n= 2)
Genotype 1 (n=91)				
ETR ; n, (%)	40/63 (63.5%)	9/14 (64.3%)	6/14 (42.9%)	0/1
SVR ; n, (%)	31/63 (49.2%)	4/14 (28.6%)	4/14 (28.6%)	0
Genotype 2 (n=5)				
ETR ; n, (%)	5/5 (100%)	0	0	0
SVR ; n, (%)	5/5 (100%)	0	0	0
Genotype 3 (n=160)				
ETR ; n, (%)	80/103 (77.6%)	10/14 (71.4%)	34/42 (81%)	0/1
SVR ; n, (%)	69/103 (67%)*	3/14 (21.4%)*	27/42 (64.3%)	0
Genotype 4 (n=3)				
ETR ; n, (%)	1/2 (50%)	1/1 (100%)	0	0
SVR ; n, (%)	0/1	0	0	0
Genotype 6 (n=1)				
ETR ; n, (%)	1/1 (100%)	0	0	0
SVR ; n, (%)	0	0	0	0

Note: 4 patients did not have HCV genotype done and were excluded in the analysis according to genotype.
ETR=end of treatment response, SVR=sustained virological response
*SVR in the HCV monoinfected between treatment naive and treatment experienced is statistically significant (P = 0.001), the rest are not statistically different.

Table VI: Univariate and Multivariate Analysis of Factors Associated with Sustained Virological Response

Factors	Univariate		Multivariate	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Naïve vs Treatment Experienced	0.192 (0.080-0.461)	<0.001	Sample size too small for analysis	
Baseline Platelet (10^3 ml/L)	1.004 (1.000-1.009)	0.033	0.996 (0.984-1.008)	0.533
HCV RNA <800,000iu vs > 800,000iu	0.504 (0.308-0.825)	0.006	0.619 (0.229-1.673)	0.344
RVR	10.924 (3.95-30.18)	<0.001	10.870 (3.866-30.564)	<0.001
EVR	66.000 (8.741-498.349)	<0.001	29.903 (3.011-296.994)	0.004

DISCUSSION

Hepatitis C patients who received treatment with PegIFN/RBV in our hospital were predominantly young males with a mean age of mid-forties. The predominant HCV genotype is 3 (60.6%) followed by genotype 1 (36.1%) and the other HCV genotypes are rare. There were clinical features indicative of a difficult-to-treat type of HCV subpopulation such as high baseline viral load above 800,000 iu/ml, liver cirrhosis and co-infection with HIV. Co-morbid illness was found in over 40% of our patients' even though they were of a relatively young age group. These are probably reflective of the sicker patients referred to a tertiary referral center in the public health system.

Blood or blood product transfusion before 1994 and injection drug use, were the two most common self-reported risk factors, however more importantly a sizeable portion of the patients (17.6%) denied having any of the frequently reported risk factors. Although the retrospective nature of this study may affect the true self-reported risk factors, this information is still important since it is representative of the "real life" scenario; when health care worker interview patients to assess who needs HCV screening in day to day clinical practice. Moreover with 15.1% of the patients having normal ALT, our HCV screening and diagnosis programs need to take cognisance of the potential pitfalls if screening is only targetted to those who possess risk factor or even abnormal ALT. Lack of clear cut risk factors were also previously reported in a systematic review of Asians with chronic hepatitis C[16].

Based on an intention-to-treat analysis, the overall SVR of this heterogenous set of patients which are typical of our routine clinical practice were 54.9%. The SVR in the two main HCV genotypes were 41.2% for genotype 1 and 62% for genotype 3. As for the other three less common genotypes the SVR was 100% for genotype 2 but none of the genotype 4 (n=3) and genotype 6 (n=1) achieved SVR. This could be due to small sample size as well as genotype 4 is known to have wide ranging SVR rates between 30 to 80% depending on the type of interleukin 28 B (IL 28 B) genes polymorphism[20]. By applying further subgroup analysis according to baseline characteristics like HIV coinfection and prior treatment status, we found in the treatment naïve HCV monoinfected, the SVR was higher for genotype 1 and genotype 3 (49.2% and 67% respectively).

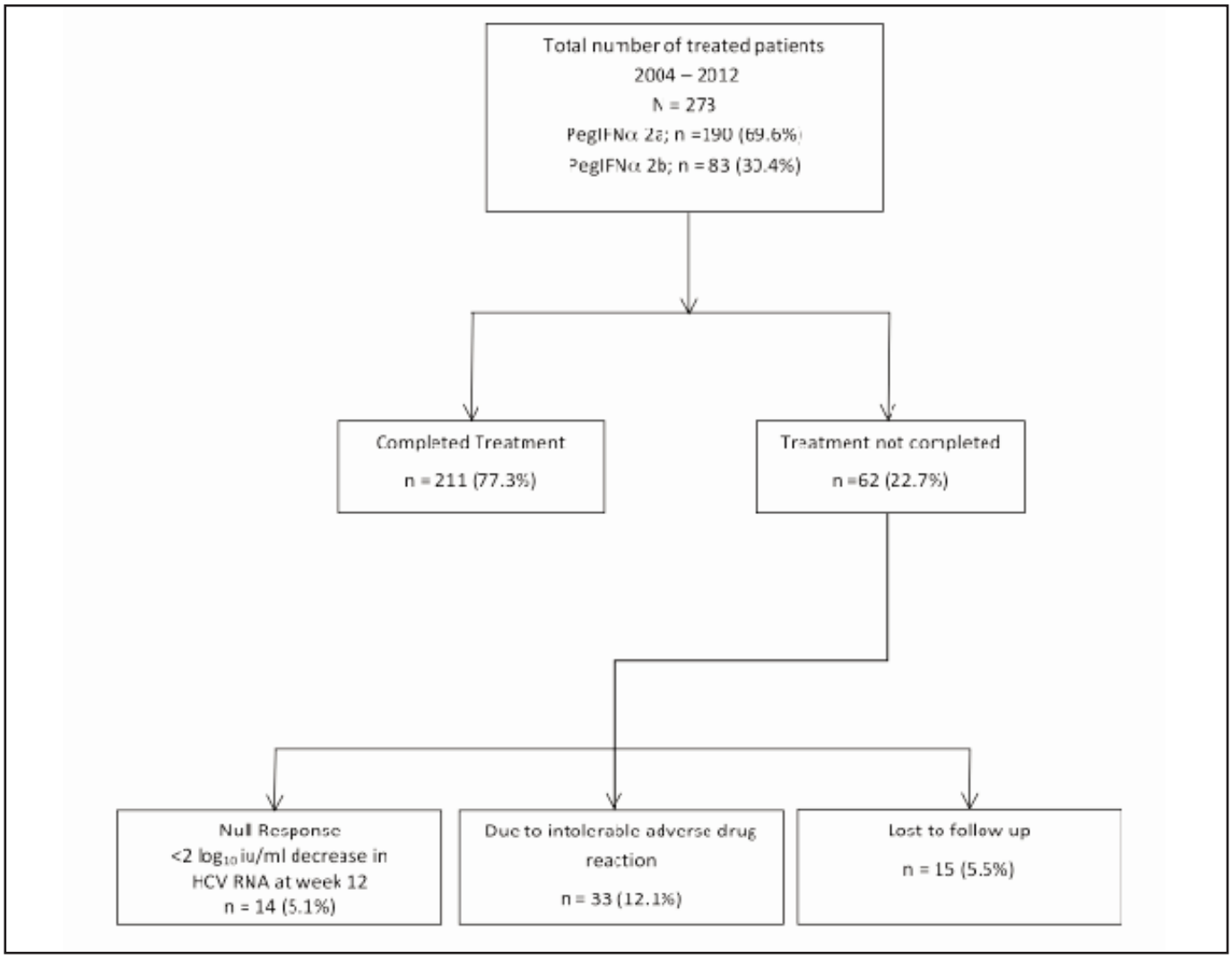

Fig. 1: The distribution of study population according to treatment completion and discontinuation.

Using longer durations of PegIFN/RBV as re-treatment strategy produced very poor SVR rates for HCV mono-infected and treatment experienced patients irrespective of HCV genotype. A poor SVR was also found in the treatment naïve HIV/HCV co-infected genotype 1 patients at 28.6% though the number of patients studied was small. However in the treatment naïve HIV/HCV co-infected genotype 3 patients the SVR of 64.3% was just as good as the HCV mono-infected at 67% (p=0.775). This could be due to the longer duration of PegIFN/RBV therapy used in the HIV/HCV co-infected group as well as a smaller percentage of cirrhotic patients (n=5/145, 3.45%) in the HIV/HCV co-infected compared to 15.9% (n=23/145) in the HCV mono-infected genotype 3 patients.

In cirrhotic HCV mono-infected or HIV/HCV-coinfected patients, the response to PegIFN/RBV is very poor, especially for HCV genotype 1 with only one third or less achieved SVR even in the mono-infected and treatment naïve cirrhotics. Although statistical analysis did not show a significant difference, this group of patients may be prioritized for DAA therapy. They have urgency for treatment due to the severity of liver disease and also due to the poor results from PegIFN/RBV.

Our study was limited in terms of its retrospective observational design resulting in some missing values however the response rates were reported as an intention-to–treat whereby all patients lost to follow-up or with missing HCVRNA at the ETR or SVR were included and assumed as non responders. Another limitation is the lack of steatosis data which is commonly associated with genotype 3 patients[13] and it had been associated with higher rates of relapse.[21] We also do not have information on the IL28B genetic polymorphism. Certain favourable polymorphisms of interleukin 28B (IL28B) gene are host factors predicting response in interferon based HCV therapy. Asians with favourable alleles to the IL28B are predictors of SVR. [16] Although a recent meta-analysis showed the association of the favourable alleles was weaker in HCV genotypes 2 and 3 infections.[22]

The strength of our data set which included all treated HCV patients over 8 years is in its true representation of a routine

daily practice typical of a tertiary referral public hospital in the country. We believe that our findings will be useful for the formulation of local guidelines and recommendations for the DAA treatment prioritization of certain HCV patients.

Hepatitis C patients of Asians ancestry had been reported to respond better to PegIFN/RBV[18] so we made comparisons to clinical trials using PegIFN/RBV on Asian patients. Our study showed lower SVR rates compared to those reported in a systematic review of Asians clinical trials, which were 61-79% for genotype 1 and 74-94% for genotype 2/3.[17] However there are numerous differences between clinical trials and routine clinical practice in terms of clinical features of patients included and treatment settings. Consequently when we compared with other routine clinical practice data, our results are more in keeping with these type of studies from Canada (treatment naive, HCV mono-infected, 5% cirrhotics, SVR as ITT for genotype 3=63.6%%, for genotype 2=74.4%)[23], Germany (treatment naive, 7.8% cirrhotics, SVR as ITT for genotype 3=47%, for genotype 2=61%)[24], Australia (treatment naïve and treatment experienced, 5 HIV/HCV co-infected, 12 HBV/HCV co-infected, 16.4% cirrhotics, SVR based on those with available SVR data for genotype 1=46.9%, genotype 2=68.8%%, for genotype 3=62.4%)[25], Korea (treatment naïve, SVR for genotype 1=53%, for genotype 2/3=71.4% but only 1.9% are of HCV genotype 3)[26] and India (treatment naïve, SVR as ITT for genotype 1=57%, for genotype 3=78.2%).[27]

A "real life" study on re-treatment with PegIFN/RBV for those who failed previous standard interferon/RBV also showed a low SVR rate in genotype 1 at 22.2% and in genotype 3 it was slightly higher at 40%.[28] Two large clinical trials on re-treatment with PegIFN/RBV showed that if the previous treatment regimen was standard IFN with or without RBV and previous relapsers had a higher chance of responding at 43%.[29,30] In this study we have a mixture of previous PegIFN and standard IFN patients, similarly the results of our strategy to re-treat with longer duration of PegIFN/RBV produced very low SVR even in genotype 3 patients at 21.4%, however the numbers of patients in these subgroups at only 14 of each genotype are small.

Various clinical studies as well as data from routine clinical practice had shown certain baseline characteristics and on-treatment responses have an effect on SVR. From the routine clinical practice data, absence of cirrhosis, genotype 2/3, female gender, low baseline viral load are positive baseline predictors of SVR while achievement of rapid and early virological responses were on-treatment features predictive of SVR.[23-27] Prediction of SVR using baseline characteristics will assist clinicians in identifying who is likely or unlikely to respond to PegIFN/RBV therapy. In this study, we found that baseline platelet counts (OR 1.004; 95% CI 1.000-1.009; p=0.033), treatment naïve (OR 0.192; 95% CI 0.080-0.461; p<0.001), low viral load (<800,000 iu/ml) (OR 0.504; 95% CI 0.308-0.825; p=0.006), achievement of EVR (OR 66.000; 95% CI 8.741-498.349; p<0.001) and RVR (OR 10.870; 95% CI 3.866-30.564; p<0.001) were statistically significant on univariate analysis but only RVR remained significantly associated with SVR on multivariate logistic analysis. (Refer Table IV)

In our routine clinical practice, the premature treatment discontinuation rate was 22.7% with the main reasons being due to intolerable AE at 12.1%, 5.1 % was due to null response and 5.5% due to patients default during or after completion of treatment. These are also comparable with other routine clinical practice data which reported discontinuation rates ranging from 8% to as high as 40% which were also mainly due to adverse effects, patient defaulting follow-up and in smaller percentage due to lack of virological response.[23-27]

PegIFN/RBV therapy has been known to cause many AEs, in registration trials 10% to 15% of study subjects discontinued treatment due to AE.[31,32] In our study a high percentage of our patients (90.1%) suffered from at least one AE but fortunately it caused a much smaller percentage of premature treatment discontinuation at 12.1%. Perhaps our multi-disciplinary approach to patient management which involved repeated patient education, counselling, dedicated single clinician for whole of treatment period and in the latter part the medication therapy adherence clinics had helped to support patients to cope with their side-effects as shown by others.[33] Although hematological AE ranked fourth in terms of frequency of AE, it is the most common AE to cause early treatment discontinuation. This maybe due to higher number of cirrhotic patients at baseline and also the lack of hematological growth factors use in our treatment program. The efficacy of treatment in our study is affected by PegIFN dose reduction but not RBV. In a prospective study of HCV genotype 1 with advanced fibrosis or cirrhosis re-treated with PegIFN/RBV, reducing the dose of PegIFN during the first 20 weeks of treatment decreased viral clearance and SVR. In contrast the SVR is not affected if the dose of ribavirin was reduced as long as patients remained on full-dose peginterferon.[34] Better tolerable HCV therapy like the interferon and ribavirin free regimen will greatly help our HCV treatment programs.

We are not able to show that PegIFN/RBV therapy has a role at par with the DAA in genotype 3 patients with RVR (SVR=85.2%), this maybe due to the small number of patients with RVR data (n=90).

In conclusion, our HCV patients with predominant genotype 3 have features of being difficult –to-treat with PegIFN/RBV. The treatment is safe in our routine clinical practice. Its efficacy although lower compared to the reported Asian clinical trials setting, are comparable to some of the routine clinical practice results from various regions. From our results, the treatment naïve cirrhotic HCV mono-infected and HIV/HCV-coinfected patients, especially for HCV genotype 1 and PegIFN/RBV treatment experienced are priority cases to be considered for DAA.

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