IMPROVING CLINICAL OUTCOMES IN VIRAL HEPATITIS B AND C REALTED CHRONIC LIVER DISEASE BY LAMIVUDINE WITH ADEFOVIR SALVAGE THERAPY AND PEGYLATED INTERFERON BASED REGIMEN: SINGLE CENTRE EXPERIENCE

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ABSTRACT

Background and Aims: Chronic Hepatitis B (CHB) and C (CHC) lead to chronic liver disease and complications if left untreated. Our study was to evaluate antiviral therapy for both CHB and CHC on clinical outcomes and liver related complications.

Methods: Eighty-three CHB and twenty-one CHC patients were included. Inclusion criteria were HBVDNA>10^5 copies/ml, abnormal Liver Function Tests (LFTs), cirrhosis and positive HCVRNA. Daily Lamivudine with/without Adefovir rescue therapy and Pegylated Interferon with Ribavirin were prescribed. Exclusion criteria were hepatocellular carcinoma, renal failure, and CHB/CHC/HIV co-infection. Outcomes measured were: proportion of patients who i) normalize LFTs, ii) achieve sustained virological remission, iii) improve Child-Pugh (CP) score, iv) develop liver related complications and v) die.

Results: CHB: Thirty-one patients (37%) had baseline cirrhosis. The mean therapy duration was 67.5 months. At the end of study, 100% had undetectable HBVDNA and 98% had LFTs normalization. The majority (87%) had stable C-P score, of whom 11.42% had improvement of score >2 points. Lamivudine resistance developed in 59.5% requiring add-on Adefovir therapy. Only eleven patients (13%) developed complications. CHC: There were 21 patients (genotype1=62%). Eight patients (38%) had baseline cirrhosis. LFTs improved in 18 patients (86%). The overall end-of-treatment response and SVR were 95% and 86% while SVR for genotype 1 and 2/3 were 92% and 75% respectively. No major liver related complications or mortality were noted.

Conclusion: Antiviral therapy resulted in excellent clinical outcomes with disease complication free in 87% of CHB and 100% of CHC patients.

Keywords: *Hepatitis treatment, Lamivudine, Adefovir, clinical outcomes, liver cirrhosis, HCC*

1. INTRODUCTION

Viral Hepatitis B and C lead to significant morbidity and mortality from chronic liver disease including HCC afflicting 400 and 170 million people worldwide respectively[1]. The risk of becoming chronic liver disease depends upon the mode of acquisition, the age of the individual at the time of infection and the receipt of treatment[2]. Development of cirrhosis and disease progression lead to liver decompensation and complications such as hepatocellular carcinoma, bleeding varices, ascites, encephalopathy, spontaneous bacterial peritonitis, and hepatorenal syndrome[3]. Decompensation results in frequent hospitalizations with increased use of healthcare resources, increased mortality or requirement for liver transplantation ultimately in appropriate cases[4,5]. Suppression of viral load by antiviral treatment could lead to the improvement in clinical outcomes and reduction of complications of cirrhosis and they were demonstrated by the CALM (Cirrhosis And Lamivudine Monotherapy) study.[6] The transition from clinical studies to clinic management can be variable due to prioritisation for health care resources in each individual country. In Singapore, the Health Services Development Program (HSDP)[5] was intended to fund three categories of programs – new cutting edge medical technologies which require a period of evaluation, advanced and experimental treatments which require a period of evaluation and major augmentations of existing management capability for key diseases. Consequently, in 2002, a HSDP grant to evaluate the efficacy of treatment of chronic viral hepatitis B and C was awarded.

Initially, our HSPD grant study was proposed for three years but was extended for another five years. We observed clinical outcomes and complications developed highlighting the treatment would lead to improve outcomes and minimize or prevent the complications of the chronic liver disease from viral hepatitis.

2. MATERIALS AND METHODS

This was a prospective cohort study to evaluate the clinical improvement and outcomes of the chronic liver disease in patients receiving antiviral treatment. Patients were enrolled into the program study if they fulfilled eligibility criteria for hepatitis B or C treatment. The patients also agreed to accept the follow up protocol. Since it was a treatment program study by approved antiviral, neither Institutional Review Board approval nor informed consent was sought. Fifty percent of cost of medication and follow up investigations were reimbursed. Descriptive analysis on clinical improvement, outcomes and complications was performed.

2.1 Hepatitis B

Following patients were considered eligible for therapy if they fulfilled the proposed criteria: HBsAg positive for 6 months, HBV DNA > 10^5 copies/ml and abnormal ALT, or had evidence of liver cirrhosis. Patients were excluded if they had hepatocellular carcinoma, renal failure or co-infection with hepatitis C or HIV. Diagnosis of cirrhosis was made by HBS ultrasound or liver biopsy. Those with active cirrhosis or decompensated liver disease were assessed by liver scanning, histology and/or liver function tests, and Child Pugh scoring system.

Patients were treated with Lamivudine 100mg daily. They were monitored 3 monthly with HBV DNA,

liver function tests, AFP and 6 monthly with HBS ultrasound. Child Pugh score was monitored every 3 months in those with cirrhosis. Patients who developed HBeAg seroconversion during this period (in patients who were initially HBeAg positive) were allowed to stop therapy after additional 6 months therapy. For patients who developed breakthrough HBV DNA (positive DNA on 3 occasions at least 1 month apart) and evidence of Lamivudine resistance mutations, Adefovir dipovoxil was prescribed.

2.2 Hepatitis C

Following patients were considered eligible for therapy if they fulfilled the proposed criteria: anti-HCV positive, HCV RNA positive and abnormal ALT, histological evidence of liver inflammation/fibrosis or had evidence of liver cirrhosis. Patients were excluded if they had hepatocellular carcinoma, renal failure or co-infection with hepatitis B or HIV. Diagnosis of cirrhosis was made by HBS ultrasound or liver biopsy. Pre-treatment evaluation included Child Pugh score if they had evidence of cirrhosis.

Patients suitable for therapy received 12 months of Pegylated Interferon weekly and ribavirin daily for genotype 1 patients and 6 months treatment for genotype 2/3 patients. Patients were reviewed weekly in the first month and monthly until the end of treatment. Thereafter, patients were seen 3 monthly. Patients who had negative HCV RNA 6 months after the end of treatment were considered to achieve sustained virological response (SVR).

The following outcomes were monitored for both hepatitis B and C: i) number of patients who improve LFTs, ii) number of patients who achieve negative HBV viral load / sustained virological response, iii) number of patients who improve Child Pugh score, iv) number of liver related hospitalisation episodes, v) number of liver related complications, vi) mortality.

3. RESULTS

3.1 Hepatitis B

A total of 83 patients were included in the study and followed up for an eight year period from 2002 to 2009. The majority of the patients were male (n=60, 72%) with mean age of 45.2 years (95% CI 42.4 - 48 years). Less than half of the patients (n=31, 37%) were cirrhotic at the entry. They were Child-Pugh A (n=25, 81%) and Child-Pugh B (n=6, 19%). The baseline characteristics are shown in Table (1).

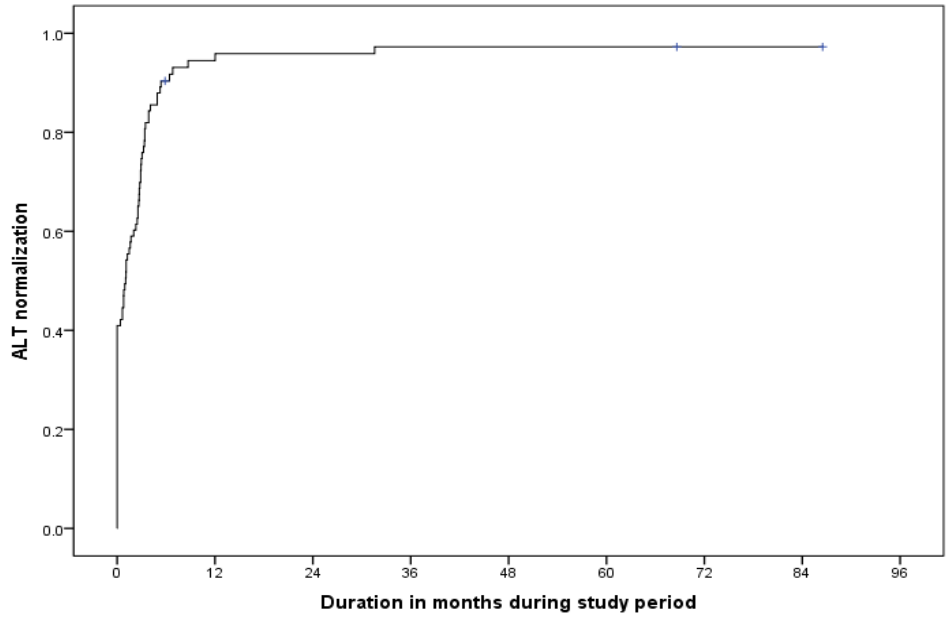
Table (1) Demographic and baseline clinical characteristics of treated hepatitis B patients

	HBeAg + (n=58)	**HBeAg – (n=25)**	**Total (n=83)**
Male	38 (65.5)	22 (88.0)	60 (72.3)
Chinese	57 (98.3)	24 (96.0)	81 (97.6)
Cirrhosis	16 (27.6)	15 (60)	31(37.3)
Age (years)	41.1 (38.1-44.0)	54.8 (50.4-59.3)	45.2 (42.4-48.0)
Alb (g/L)	39 (38.4-41.0)	37 (34.5-40.3)	39 (37.8-40.2)
Bil (umol/L)	18 (10.1-26.7)	19 (12.0-26.0)	18 (12.5-24.6)
AST (U/L)	147 (96-199)	112 (40-184)	137 (96-178)
ALT (U/L)	237 (156-317)	138 (60-216)	207 (146-268)
ALP (U/L)	92 (83-102)	119 (83-156)	100 (88-113)
LDH (U/L)	548 (507-590)	549 (454-645)	549 (509-588)

DNA (log cps/ml)	7.0 (6.7-7.4)	6.2 (5.7-6.7)	6.8 (6.5-7.1)
Categorical data shown in number (%), continuous data in mean (95%CI)			

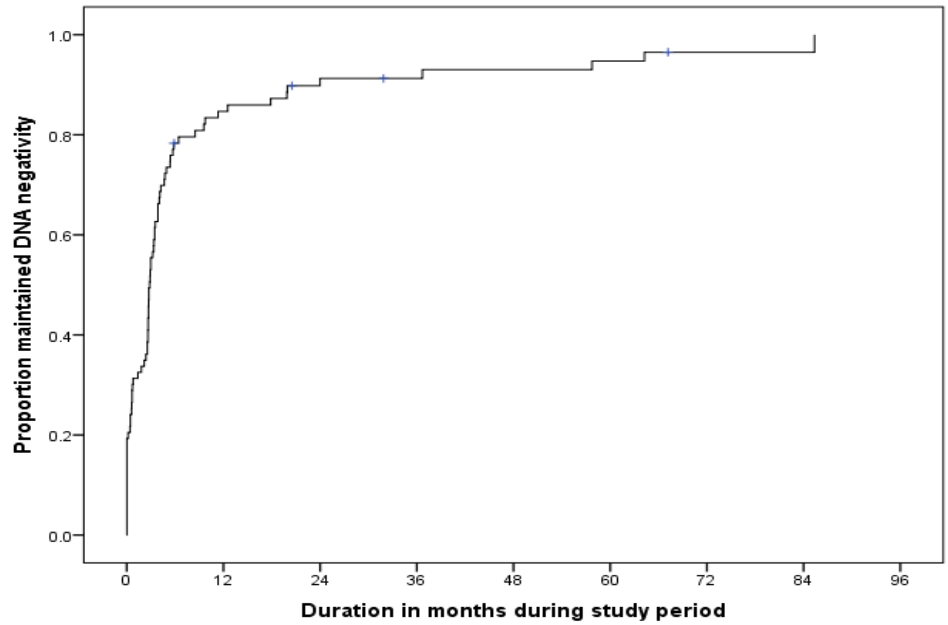
Categorical data is shown in number (%), continuous data is shown in mean (95%confidence intervals). Alb= serum albumin, Bil = Serum bilirubin, ALT= serum alanine aminotransferase, AST= serum aspartate aminotransferase, ALP = serum alkaline phosphate, LDH=lactate dehydrogenase, DNA=HBV DNA

Figure (1) ALT normalization in treated hepatitis B patients



Kaplan Meier graph showing normalization of liver function tests in treated hepatitis B patients over 8 years

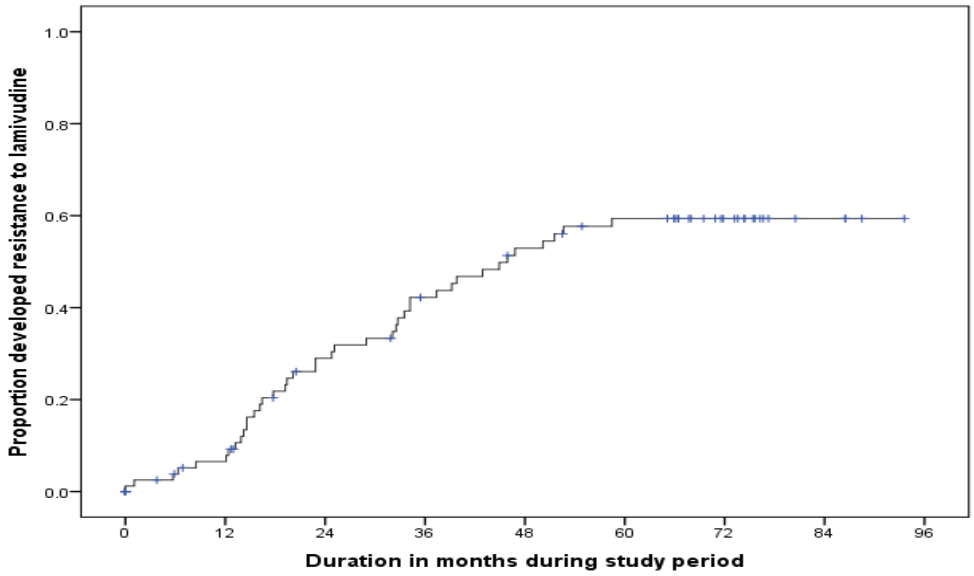
Figure (2) Maintaining HBV negativity in hepatitis B patients



Kaplan Meier graph showing maintained HBV DNA negativity in treated hepatitis B patients over 8 years

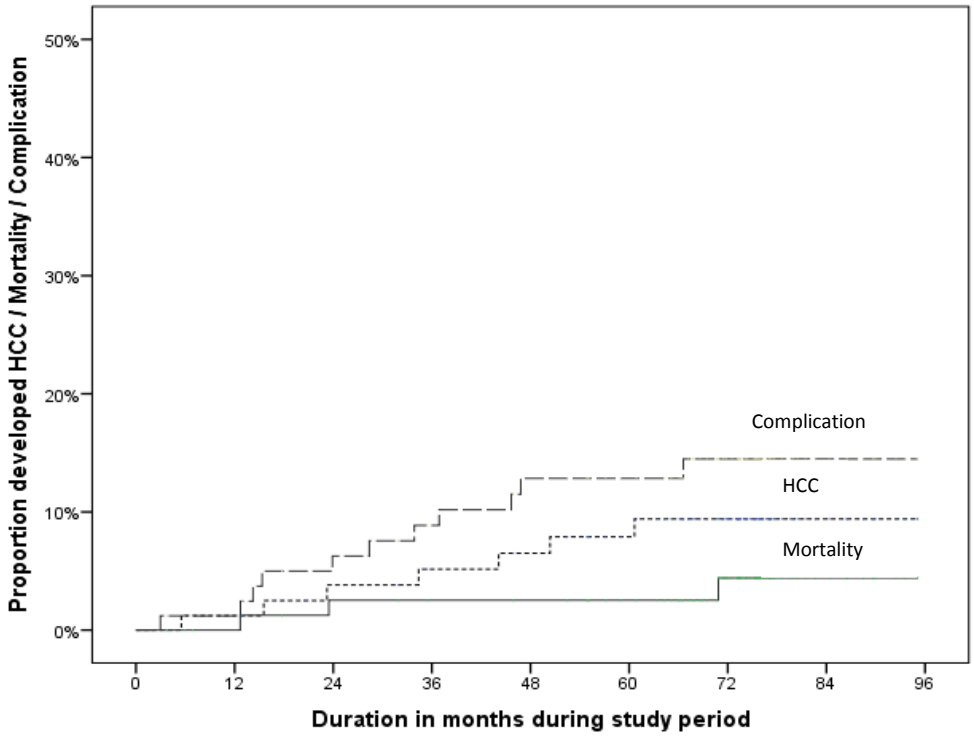
Ninety five percent of patients normalized their liver function tests by 12 months and at the end of 8 year study, 98% of patients achieved normalization. (Fig. 1) Significant hepatitis B viral load reduction was seen during the study achieving 94.8% and 100% undetectable DNA by the end of 5 and 8 years respectively (Fig.2) Most of cirrhotic patients (n=27, 87%) had stable Child-Pugh of whom 11.42% (n=4) had improvement in Child-Pugh score >2 points.

Figure (3) Development of resistance in all patients



Kaplan Meier graph showing the development of anti-viral resistance among treated hepatitis B patients over 8 years

Figure (4) Development of complications and mortality during the study period



Kaplan Meier graph showing the development of complications and death among treated hepatitis B patients over 8 years

At the end of the study period, a total of 41 (59.5%) patients developed cumulative Lamivudine resistance. (Fig. 3) All patients who developed resistance to Lamivudine were rescued by addition of Adefovir. Among them, twelve patients (14.46%) failed to achieve complete viral suppression and had Entecavir either as additional therapy to Adefovir or switching therapy.

Eleven patients (13%) developed liver related complications (Fig.4) despite achieving undetectable HBVDNA with therapy during the study period. Six patients developed HCC at a cumulative rate of 9.7% over 8 years, one patient developed hepatitis B flare while the others developed complications of chronic liver disease such as variceal bleeding (n=2), encephalopathy (n=3) and ascites (n=2). One HCC patient underwent liver transplantation. One patient (1.2%) died from end stage liver disease and two patients died from other medical conditions.

3.2 Hepatitis C

Twenty one patients were included in the study after excluding two patients who were lost to follow up after having one week of treatment. Majority of the patents in the study were male (n=16, 76%). The majority of patients were Chinese (n=17, 81%) and the remainders were Malay, Indian and Myanmar. Genotype 1 patients were found to be older (52 years) than genotype 2 and 3 patients (41years). Genotype 1 was the predominant genotype (n=13, 62%) among the study population with equal number of patients in other groups (4 patients each in genotype 2 and 3). Baseline characteristics including liver function tests, status of liver cirrhosis and Hepatitis C RNA level are shown in Table (2).

Table (2) Demographic and baseline characteristics of Hepatitis C patients

	Genotype 1 (n=13)	**Genotype 2 (n=4)**	**Genotype 3 (n=4)**	**Total (n=21)**
Male	10 (76.9)	4 (100.0)	2(50.0)	16 (76.2)
Chinese	10 (76.9)	4 (100.0)	3 (75.0)	17 (81.0)
Cirrhosis	5 (38.5)	1 (25.0)	2 (50.0)	8 (38.1)
Age(years)	52.1 (47.1)	41.4 (22.2)	41.9 (10.3)	49.3 (47.1)
Alb (g/L)	40.0 (15.0)	40.0 (3.0)	40.0 (11.0)	40.0 (15.0)
Bil (umol/L)	11.0 (57.0)	11.5 (30.0)	10.5 (34.0)	11.0 (57.0)
ALT (U/L)	83 (200)	86 (347)	112 (107)	87 (347)
ALP (U/L)	78 (339)	82 (18)	73 (20)	78 (339)
LDH (U/L)	524 (468)	491 (199)	583 (393)	521 (564)
RNA (log cps/ml)	6.2 (2.5)	6.5 (0.8)	6.3 (1.2)	6.4 (2.5)

Categorical data shown in number (%), continuous data in median (range)

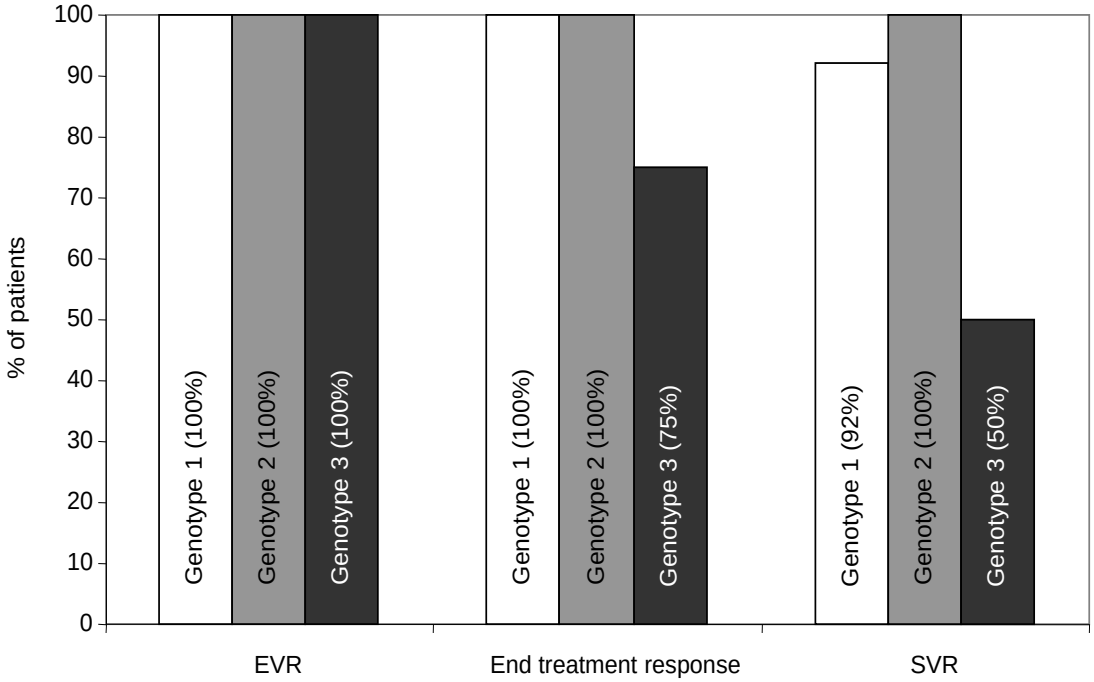
Alb= serum albumin, Bil = Serum bilirubin, ALT= serum alanine aminotransferase, AST= serum aspartate aminotransferase, ALP = serum alkaline phosphate, LDH=lactate dehydrogenase, RNA=HCV DNA

Eight patients (38%) were found to have cirrhosis at the start of the study and cirrhosis was confirmed by liver biopsy in most of the cases. Cirrhotic patients belonged to Child-Pugh A (n=4) and B (n=4). Improvement in Child-Pugh score was seen in two patients whose Child-Pugh score improved from B to A as a result of

treatment. Improvement in liver function tests were also seen in 18 patients (86%). Twenty patients (95%) achieved end of treatment response (ETR). While genotype 1 (n=12) achieved SVR of 92%, genotype 2/3 (n=6) achieved SVR of 75% (genotype 2=100% and genotype 3=50%) resulting in initial overall SVR of 86%. Two patients who failed initial therapy were retreated with the same dose of interferon and ribavirin (genotype 1 and genotype 3). Both achieved SVR after a further one year of retreatment resulting in final overall SVR of 95% (genotype 2/3 88% and genotype 1 100%).

During the treatment period, only two patients were admitted to the hospital for blood transfusion for anaemia. No major liver related or treatment related complications including mortality were noted during the follow up period.

Fig (5). Treatment response with hepatitis C genotype



Bar graph showing the outcome of the treated hepatitis C patients in number (%). EVR= Early Virological Response, SVR= Sustained Virological Response

4. DISCUSSION

Chronic hepatitis B infection is one of the major health problems in many parts of the world especially in Asia. The clinical presentation during chronic disease ranges from an asymptomatic carrier status to chronic hepatitis, cirrhosis and its complications including hepatocellular carcinoma and these can be reduced by antiviral therapy.[7,8,9]. At the time of the study, Lamivudine was the standard of care despite its high viral resistance profile. Lamivudine with addition of Adefovir was the standard salvage therapy when lamivudine resistance developed since Tenofovir was not available in the market.[10] This antiviral combination may still be the choice of treatment in some parts of the Asia due to the cost reason.

The objective of our study was to provide antiviral therapy to chronic hepatitis patients and evaluate the clinical improvement and outcomes. For chronic

hepatitis B, 98.4% and 100% of patients achieved normalisation of LFTs and complete suppression of HBV DNA respectively at the end of 8 year study period though 59.5% of patients developed cumulative resistance to Lamivudine. The resistance rate was lower than that of one long- term case control study (76.3%) with median treatment duration of 8 years.[11]

In our study, 11 patients (13%) had liver related complications. Most of them (n=6, 55%) were baseline cirrhotic or developed cirrhosis (n=3, 27%) showing disease progression despite negative viral counts with treatment. There were 6 patients who developed HCC and majority (n=5, 83%) were cirrhotic. The cumulative rate of HCC in our study were comparable with other studies. In one study, patients treated with lamivudine for more than 1 year developed HCC at the rate between 4.9% to 19.4% depending on level of viral suppression and response[12]. Our previous study with over 5 years treatment showed HCC rate of 15.9% with the mean survival, ascites, encephalopathy and deterioration in Child-Pugh score of 83.6%, 7%, 10.8% and 16.9% respectively. In that study, 32.8% of patients progressed to liver disease complications in spite of effective antiviral therapy[13]. Patients with advanced liver cirrhosis progressed more rapidly and had a high mortality in the first 12 months of therapy. In another European study, patients with compensated hepatitis B liver cirrhosis who received Lamivudine with Adefovir salvage therapy with mean follow up of 27.6 months developed HCC (16.12%), decompensation (16.12%) and liver related death (12.9%)[14]. It clearly demonstrated in our study as well as other studies the limited benefit of antiviral therapy in preventing complications especially in advanced liver diseases.

Chronic Hepatitis C is one of the causes of chronic liver diseases in the East but less prevalent compared to the West. There is increasing evidence that Asians have a higher likelihood of achieving a sustained virological response (SVR) than their Caucasians counterparts when treated with the corresponding regimen. In Asia, with the standard dose and duration of treatment regimens, SVR of approximately 70% is achievable for HCV genotype 1 (HCV-1) infected cases, 90% for HCV-2/3, 65% for HCV-4 and 80% for HCV-6 patients. A difference in body weight and race may contribute to the superior response in Asian patients[15] and it seems this improved response is likely due to the higher prevalence of the IL-28B CC genotype[16]. In our study, genotype 1 patients achieved highest SVR (92%) and genotype 3 patients achieved lowest SVR (50%). It was hard to interpret the results for genotype 3 since the numbers of patients were small in that group but it is now understandable from emerging evidences for genotype 3 being difficult genotype to treat. End-of-Treatment response was seen in 20 patients (95%). Though we did not analyse the response with fibrosis or steatosis status, It is clear from some studies that poor responses were seen in patients with advanced fibrosis,[17] significant steatosis[17,18] or patients who do not achieve rapid virological response (RVR).[19]

There were 3 patients (2 patients in genotype 3 and 1 patient in genotype 1) failed the treatment. Among them, one patient with genotype type 3 had partial response but re-treatment was not possible due to costs issue as well as poor tolerability from end stage renal failure. The remaining two patients were relapsers and both achieved SVR after retreatment resulting in final overall SVR of 95%. None of these patients developed any long term complications following their SVR although 38% of patients were cirrhotic

clearly demonstrating achieving SVR improves clinical outcomes in hepatitis C patients.

5. CONCLUSION

Our study clearly showed Lamivudine with addition of Adefovir as the salvage therapy was an excellent choice for achieving complete (100%) viral suppression and improvement in clinical outcomes with disease free complication in majority (87%) of hepatitis B patients. This choice of antiviral therapy is likely to be cost effective in places where the expensive new antiviral therapy puts huge financial burden on patients as well as on healthcare system. Likewise, despite availability of expensive new DAAs, Pegylated Interferon and Ribavirin therapy in our study showed final overall SVR of 95% after retreatment of two relapsers. The study also demonstrated that antivirals have limited benefit in patients with advanced liver diseases who developed complications despite therapy and concluded that therapy should be initiated before the disease is advanced.

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