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Chronic hepatitis C treatment response to combination therapy: Experience of RIPAS Hospital

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ABSTRACT

Introduction: Chronic hepatitis C (CHC) infection is an important cause of chronic and end stage liver disease. Treatment response has improved with combination therapy. We review our experience with combination therapy in CHC patients. **Materials and Methods**: All patients who had completed at least one course of combination therapy (> 6 months) and had longer than 6 months of follow-up were retrospectively reviewed. **Results**: There were 28 (22 males, mean age 40.7 ± 9.9 years old) patients who completed one course of treatment. Intravenous drug use (IDU) accounted for 61% of the aetiology. The end of treatment biochemical response was 92.6%. The overall sustained viral response (SVR) was 64.3%. Comparing IDU to the others (non-IDU), there was no difference in treatment SVR (64.7% vs. 63.6%, p = 0.954). Responders had significantly higher pretreatment serum alanine aminotransferase (p = 0.018). Overall treatment side effects were observed in 64% (flu-like symptoms 58.3%, haematological 50% and depressive mood 8%). **Conclusions**: Our response rates are comparable to published data. There was no difference in treatment response rate between the IDU and non-IDU. CHC infected IDU should be offered treatment.

Keywords: viral hepatitis, treatment response, outcomes

INTRODUCTION

Chronic virus hepatitis is an important cause of liver diseases and left untreated in a proportion can lead to significant liver damage, cirrhosis and related complications.[1] In the Asia-Pacific region, chronic hepatitis B infection represents the most common cause of virus hepatitis followed by chronic hepatitis C infection (CHC).[2] This situation is also true in Brunei Darussalam and the main risk factor is intravenous drug use (IDU).[3] With the introduction of the combination therapy of interferon and ribavarin, response rates have improved.[4] We present our earlier experience with combination therapy consisting of standard interferon or pegylated interferon with ribavarin among patients with CHC treated in our hepatology clinic in RIPAS hospital.

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MATERIALS AND METHODS

Patients under the follow-up of the Hepatology clinic, Department of Medicine, RIPAS Hospital for CHC infection and who had undergone treatment (up till December 2004) were retrospectively identified from the clinic registries. Only patients who had completed at least a course of treatment and had at least six months of follow-up were included in the study. During this time, the treatment available included a combination of standard interferon (Intron A®, one to three million unit subcutaneous daily, Schering Plough, Switzerland) or pegylated interferon (Peg-Intron®, 80 to 100 mcg weekly, Schering Plough, Switzerland) with ribavarin (800 to 1200mg daily, Rebetron®, Schering Plough, Switzerland). Treatment regime ranged from four months to 12 months depending on the viral load. All patients were given advice regarding side effects of treatment.

Patients' clinical notes were retrieved and retrospectively reviewed. The laboratory result system was also used to retrieve the biochemical, haematological and virological investigations. Demographic data (age, gender, ethnic group and risk factors for CHC infections), clinical data and treatment response outcomes (end of treatment biochemical response [ETR] and sustained viral response [SVR]) were collected using a predefined proforma.

ETR is defined as serum alanine aminotransferase (ALT) normalisation and SVR defined as negative serum HCV RNA based on polymerase chain reaction (PCR) testing. We also assessed the necro-inflammatory marker trend based on the serum ALT trends observed over the follow up before treatments. Only patients with at least two serum ALT readings were included in the study. The histological assessments were based on the METAVIR scoring system; grade (necro-inflammatory index) 0 to 3 (0: no inflammatory activity, 1: mild activity, 2: moderate activity and 3: severe activity) and stage (fibrosis) 0 to 4 (0: no fibrosis, 1: portal tract expansion, 2: fibrosis extension, 3: bridging incomplete nodule formations and 4: nodules and frank cirrhosis).[5]

The data were coded and entered into the Statistical Program for Social Science (SPSS, version 10.0, Chicago, Il, USA) for analysis. We compared the differences between the various risk factors for CHC infections. Level of significance was taken when $p < 0.05$.

RESULTS

There were 28 patients studied with a mean age of 40.7 ± 9.9 years old. The most common risk factor for CHC infections was IDU (60.7%). The demographic is shown in Table I. Co-infection with hepatitis B virus was detected only in one patient (3.6%).

Only 23 patients had available data to assess serum ALT trends. These showed fluctuations and persistent elevations in four (17.4%) and 19 (82.6%) respectively. Liver biopsy was done in 11 patients (39.3%) prior to treatment and the histological findings showed majority had grade 2 (36.4%) and 3 (36.4%) inflammations and stage 3 (54.5%) fibrosis (Figure 1). None of the patients had stage 4 or frank cirrhosis.

Among these patients; 23 had combi-

Table 1: Demography of patients.

Variables	n (%)
Gender	
Male: female	22 (78.6): 6 (21.4)
Ethnic group	
Malay: Chinese: Others	25 (69.3): 2 (7.1): 1 (3.6)
Risk factors for Chronic Hepatitis C	
Intravenous drug use	17 (60.7)
Others	3 (10.7)
Unknown	8 (28.6)
Ethanol use	
Yes: No: Unknown	2 (7.1): 22 (78.6): 4 (14.3)

bination standard interferon/ribavarin and five had combination pegylated interferon/ ribavarin. Overall, ETR was observed in 25 patients (92.6%) and SVR was observed in 18 patients (64.3%) (Figure 2) Overall side effects of treatment were seen in 64% (flu-like symptoms 58.3%, hematological 50% and depressive related 8%).

Responders had significantly higher pretreatment ALT (p=0.018). Comparing IDU to the others (non-IDU), there was no difference in treatment response (64.7% vs. 63.6%, p=0.954).

DISCUSSION

CHC is an important cause of chronic liver disease not just in the developed nation but also in many developing nations. CHC is the leading cause of end stage liver disease, hepatocellular carcinoma and liver transplantations in the West.[2] In our local setting, CHC is the second most common cause of liver disease after chronic hepatitis B virus infection.[5] Similar to what has been reported, we also found that IDU is the most common risk factor CHC.[3] In our setting, people who have been incarcerated for IDU are routinely tested for CHC in addition to hepatitis, human immu-

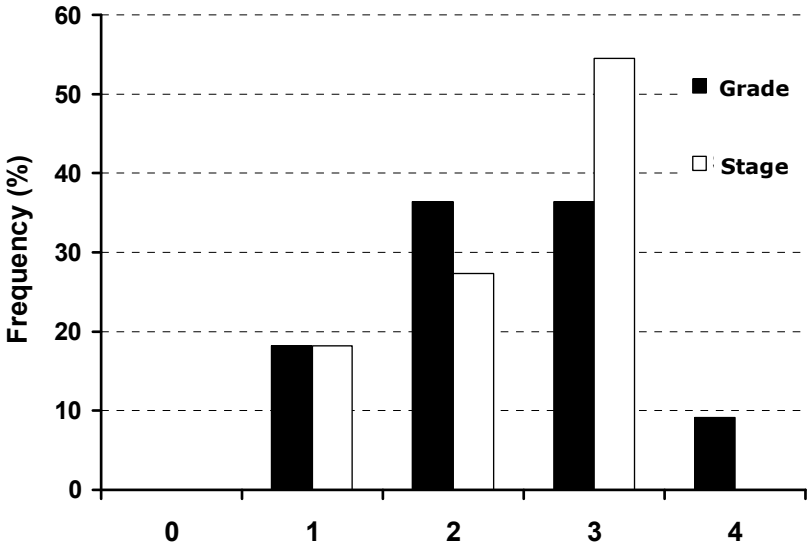

Fig 1: Histological findings of patients who had biopsies before treatment.

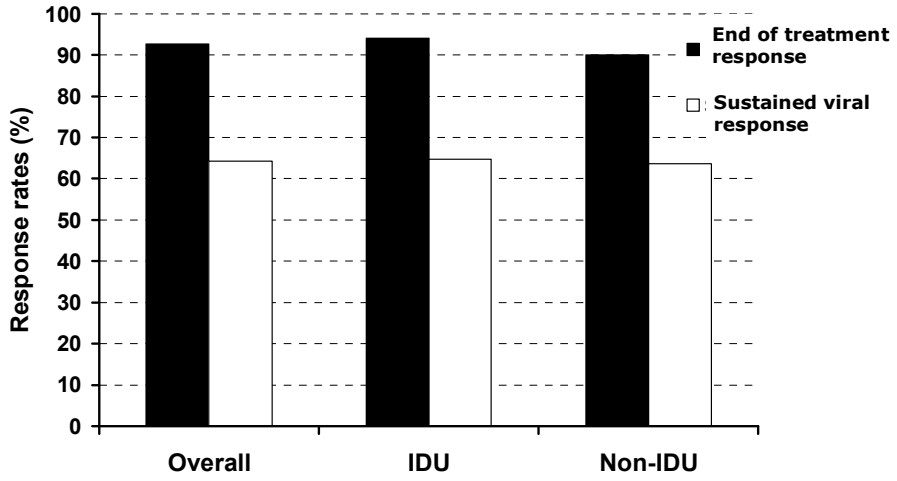

Fig. 2: Response rates of the patients.

nodeficiency virus and syphilis. Those found to be positive for CHC are routinely referred to our clinic for further management. Our study showed our treatment responses are similar to what has been reported in the literatures.[4, 6-8] Importantly, we also showed that there was no difference in the treatment response between IDU and non-IDU.[9] This is important as there is concern regarding treating this group of patient. However in our study, most of the patients had been treated with combination therapy of standard interferon/ribavarin. This was later changed to the use of pegylated interferon following the evolving trends and recommendations based newer evidences. Our high ETR is consistent with what has been reported in the literature. However, we had used serum ALT instead of the standard RNA by PCR to assess the ETR response. Therefore, if we had used PCR to assess the RNA, it was likely that our ETR would have been lower. Importantly, our SVR based on PCR RNA was comparable to published data. In fact our result was in the upper range of reported response rate for combination using standard interferon. Treatments with pegylated interferon and ribavarin therapy have been reported to have better treatment responses with fewer side effects.

Table 2: Comparison between intravenous drug use (IDU) and non-IDU groups.

Variables	IDU	Non-IDU	p values
Mean age (yrs)	37.1 ± 6.7	46.2 ± 11.7	0.025
Serum ALT (U/L)	110 ± 64	162 ± 204	0.079
Serum albumin (gm/L)	43 ± 2.7	39.7 ± 3.7	0.026
Serum bilirubin (mmol/L)	15.2 ± 6	15.9 ± 10.8	0.738
Serum ALP (U/L)	100 ± 93	86 ± 53	0.784
Serum GGT (U/L)	51 ± 29	77 ± 51	0.208
Serum protein (gm/L)	79.8 ± 4.7	76.7 ± 3.7	0.186
Histology			
Grade	2.5 ± 0.6	2.3 ± 1.1	0.788
Stage	2.3 ± 0.5	2.4 ± 0.9	0.527

ALT: alanine aminotransferase, ALP: alkaline phosphatase, GGT: gamma glutamyltransferase

There are several explanations for the high SVR observed in our experience. First, a large proportion of our patients were IDU who consisted mainly of younger patients and this is a favourable factor. However, male gender is a less favourable factor. Being IDU and incarcerated, the treatments of our patients were supervised and therefore, compliance was not a major problem. Furthermore, these patients were undergoing rehabilitation, therefore, reducing their risks for re-infections. Second, only a small proportion of our patients had reported ever using alcohol. Although, this could be underestimation of the true incidence. Active use of alcohol had been shown to reduce treatment compliance, treatment response and is associated with disease progression.[10] Finally, none of our patients had histological cirrhosis and cirrhosis has been shown to be associated with poor treatment response.[11]

Genotypes have been shown to be important factors in predicting treatment outcomes. Hepatitis C virus can be subdivided into seven genotypes from 1 to 7. Genotypes 1, 2 and 3 are the predominant genotypes worldwide and are found in most regions. However, certain genotypes predominate in certain regions. Genotypes 1 is the predominant genotype found in the West and Japan whereas genotypes 2 and 3 is the predominant types in the East. Genotype 4 is usually found in Egypt and Middle East. Genotypes 2 and 3 are the favourable genotypes compared to the others in terms of treatment responses. Asian ethnicity has also been shown to have better treatment response than Caucasians.[12] We had previously looked at the viral genotype distribution in our local setting. Our study had shown that more than two-third of our CHC patients had favourable genotypes that consisted of genotypes 2 and 3.[3] This is also an important factor that is associated with favourable response to treatment with combination therapy.

The most common side effects reported by our patients was flu like symptoms followed by haematological abnormalities. Most are easily managed with symptomatic treatment. Again, our side effects rates are comparable to reported in the literature.[4, 6-8]

There are several limitations with our study. First, the small sample size. However, the population demographics were similar to our national demographic. Another limitation is the small sample size of patient who had been treated with combination pegylated interferon and ribavarin therapy. Use of standard interferon has largely been replaced by pegylated interferon which is now considered the standard. The main reason was mainly because our study had looked at the earlier period when standard interferon was still the standard in our setting. Our study showed that with supervised treatments in the real life situations, the response rate were comparable to those obtained in randomised clinical trials where patients are monitored carefully under strict trial conditions. Studies with pegylated interferons have shown better results compared to standard interferons. Therefore, we would probably expect better response rates when extrapolated to patients treated with pegylated interferon. However, this will require further confirmation with studies looking at pegylated interferon combination in our local setting. As there is currently no data available in our local setting, our result will serve as baseline for comparison for future

studies.

In conclusion, our earlier experience with combination therapy for CHC infection using mostly standard interferon is comparable to what has been reported. However, furthur studies are required looking at larger sample size and assessing the treatment responses with combination pegylated interferon and ribavarin therapy.

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