Original Article

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Evaluation Study of Patients Infected with Chronic Hepatitis C in Iraq

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ABSTRACT

Background : Hepatitis C virus (HCV) is a major cause of chronic liver disease Approximately 85% of patients acutely infected with HCV progress to chronic liver disease with persistence of HCV RNA for more than 6months Among patients with chronic HCV infection , 15_20% progress to end-stage liver disease main transmission methods of the virus is by : blood and blood products ; sharing needles and acupuncture .
Objective : To evaluate Iraqi patients infected with chronic HCV ,including their treatment, factors that affect their response to treatment . **Setting :** This study was performed Gastroenterology and Hepatology hospital in Baghdad. **Patients and Methods :** The study enrolled 90 patients with HCV Ab +ve , every patient subjected to thorough history taking and clinical examination, and complete investigations , some of the patients subjected to liver biopsy which is analyzed by Ishak classification , the data analyzed by chi square and P value <0.05 considered statistically significant , patient age range from 18-63,mean age 41.4 year .All these patients were treated with peg interferon alpha2a given once weekly and ribavirin given in two doses daily and follow up the patients during treatment regimen. **Results :** 90 patients, 66(73.3%) patients were male,24(26.7%) patients were female were included in study .The predominant genotype is genotype 1:45 (50%) patients , genotype 4:33(36.7%) patients . Only 27(30%)patients have viral load >600000U\ml while 63(70%)Patients have viral load<600000U\ml .34(37.7%) patients showed End treatment virological response .39 (42.2%) patients had been subjected to liver biopsy including those genotype 1and4.There was asignificant association between viral load and liver enzymes .
No significant correlation between end treatment virological response with age , histopathological stage .**Conclusion :** There is a relatively low complete response to the treatment regimen for hepatitis C . Most of our patient with hepatitis C are discovered accidently, Most of them are male , young or middle age , asymptomatic or have minimal symptom , have low viral load .The commonest genotype is 1(50%) followed by genotype 4(36.7%) .Early virologic response were seen in most of the patients while end treatment response were seen in only 37.78% .There is significant association between the end treatment virological response and both genotype , pretreatment viral load and Early virologic response.
Recommendation: Attempts to improve adherence to therapy and the early detection together with treatment of complications are needed to achieve better response to therapy .

Introduction:

Hepatitis C virus (HCV) infects 170 million people worldwide . HCV successfully evades the host immune response in 55% to 85% of acutely infected persons, thus leading to chronic infection .
The natural history of hepatitis C varies greatly ; reasons for this heterogeneity remain incompletely understood but are related to both viral , host , and environmental factors [1]

Epidemiology :

Initially referred to as non-A , non-B hepatitis Choo and colleagues [2] , first characterized the HCV in 1989 in the past it was responsible for more than 90% cases of post-transfusion hepatitis [3] .Chronic hepatitis C represents one of the biggest healthcare problems worldwide . Although symptoms may be mild for decades , 20% of persistently infected individuals may eventually develop serious liver disease including cirrhosis and liver cancer [4] .

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Transmission:

No identified risk factors for HCV infection during the previous six months can be identified in up to 44 percent of cases with new infections [5]. However , after careful questioning , most of these patients give a past history of high-risk behavior (such as injection drug use [6] .Blood transfusion , before the introduction of screening, and injection drug use are the most clearly documented risk factors for HCV infection. Following the introduction of anti-HCV screening of blood donors between 1990 and 1992 . The number of transfusion-related cases of HCV infection declined sharply , and currently less than 1 case occurs per 2,000,000 units transfused [7,8].Chronic hemodialysis is also associated with increased rates of HCV infection. The frequency of anti-HCV in patients on hemodialysis ranges from 11.6% in the United States to 55% to 85% in Jordan, Saudi Arabia, and Iran [9].Although amonogamous sexual relationship carries a low risk of transmission of HCV infection, the risk is higher in persons involved with multiple sexual partners , and the degree of HCV viremia HCV antibodies occur in approximately 2% of the spouses [10] .

There is no need to curtail ordinary household activities except those that might result in blood exposure, such as sharing a razor or toothbrush .Other situations that have been suggested to carry a risk for HCV transmission include certain folk medicine practices (acupuncture, ritual scarification), body piercing, tattooing, and even commercial barbering [11,12] .The risk of perinatal transmission of HCV infection is low, averaging 5.1% to 6.7% for HCV-monoinfected patients and two to three times higher for HIV-HCV-coinfected patients[13].Surprisingly high rates of HCV infection (approximately 30 percent) have been found in patients with alcohol abuse, even in the absence of other risk factors for infection [14,15].HCV may accelerate the liver injury in patients who drink heavily [16], alcohol use appears to decrease the efficacy of interferon therapy for HCV [17], and patients with alcohol and HCV-induced liver injury have a greater risk for hepatocellular carcinoma[18]

Nutural History Of Hepatitis C Virus Infection :

Most cases of hepatitis C are identified initially in asymptomatic patients who have no history of acute hepatitis C (e.g., those discovered while attempting to donate blood, while undergoing lab testing as part of an application for life insurance, or as a result of routine laboratory tests). The source of HCV infection in many of these cases is not defined, although a long-forgotten percutaneous exposure in the remote past can be elicited in a substantial proportion and probably accounts for most infections[19]

Acute Hepatitis C:

HCV accounted for an estimated 20% of cases of acute hepatitis in 2006[20]. Acute hepatitis C is rarely seen in clinical practice because nearly all cases are asymptomatic[21]

. Jaundice probably occurs in about 10% of patients with acute HCV infection, whereas 20% to 30% of patients present with nonspecific symptoms such as fatigue, nausea, and vomiting

Chronic Hepatitis C:

Most patients with chronic hepatitis C are asymptomatic before the onset of advanced hepatic fibrosis, patients who have been diagnosed with chronic infection, however, often complain of fatigue or depression[22,23]

.Chronic hepatitis C progresses to cirrhosis in 20%30% of individuals over a period of 2030years with affected subjects at high risk for liver-related morbidity and mortality. Furthermore, the rate of hepatic fibrosis progression is often accelerated in individuals with additional risk factors for liver disease such as co-infection with hepatitis B or HIV,excess alcohol consumption, obesity, insulin resistance or advancing age. Consequently ,the primary reason for commencing treatment for CHC is to prevent the development of advanced liver disease and/or related complications of hepatic decompensation, portal hypertension, variceal haemorrhage and hepatocellular carcinoma. Even in those subjects with established cirrhosis, the incidence of these clinical endpoints can be reduced by achieving viral eradication[24,25].

Diagnosis :

Diagnostic tests for hepatitis C virus (HCV) can be divided into two broad categories:

Serologic assays that detect antibodies to hepatitis C ELISA type 3.

Molecular assays that detect or quantify HCV RNA.Other investigations such as genotype testing and liver biopsy may help to predict the response to treatment and prognosis[1]

.HCV Genotyping :

Identifying the genotype of HCV can be accomplished by several methods. The most accurate method is PCR and direct sequencing of the NS5B or E1 region; however, this approach is not practical in clinical practice. HCV genotyping can be done by evaluating type-specific antibodies and has a 90% concordance in immunocompetent patients when results are compared with sequence analysis of the HCV genome[26].

Liver Biopsy :

Liver histology is useful for determining the stage of disease,excluding other causes of liver test elevation

and guiding decisions regarding treatment and surveillance.A liver biopsy can establish the presence of concomitant diseases (such as iron overload or fatty liver disease) and the degree to which these conditions contribute to the liver disease[27,28].

Treatment : The current standard of care for the treatment of HCV infection is the combination of a pegylated interferon2a administered subcutaneously once per week and ribavirin taken orally every day. *Interferons* are naturally occurring proteins that exert a wide array of antiviral, antiproliferative, and immunomodulatory effects *Ribavirin has* no direct antiviral activity, but it has synergistic effect when administered in combination with interferon include (1) enhancement of host T cellmediated immunity against viral infections, (2) inhibition of the host enzyme inosine monophosphate dehydrogenase (IMPDH), (3) direct inhibition of HCV replication) The use of boceprevir or telaprevir in combination with peginterferon, and ribavirin shown to increase the SVR in genotype 1, response rate(63-66%)[29]

.**Aim of Antiviral Therapy for CHC :**

Despite the importance of these clinical end points, in practice virological endpoints are used to define the success of anti-viral therapy . In particular, the definition of treatment success is a *sustained virological* response(SVR) that is defined by having undetectable HCVRNA 24 weeks after the cessation of treatment[30].This is invariably associated with an *end* of treatment response (ETR) that refers to having undetectable HCV RNA at the cessation of therapy. SVR is durable end point with over98%sustained responders remaining PCR negative at 5 year[31].

Factors That Predict A Sustained Virologic Response:_The best predictor of response to pegylated interferon and ribavirin is the rate of the initial fall in serum HCV RNA levels during treatment. The highest SVRs occur in patients with an RVR followed respectively by those with a cEVR, those with a pEVR, and those without an EVR. Patients are usually interested in an estimate of their chances of a response before making a decision to proceed with therapy[32].Pretreatment factors associated with a greater chance of an SVR include infection with non-genotype 1 HCV[33]

, a low baseline serum HCV RNA level, absence of bridging fibrosis or cirrhosis on a liver biopsy specimen, age younger than 40 years, absence of obesity, lack of hepatic steatosis or insulin resistance, absence of HIV infection, and white race. Although the likelihood of an SVR is marginally lower in patients without these favorable factors, patients should not be discouraged and treatment should not be withheld because of the presence of any or all of these factors[1]

Patient &methods

Between January 2011 &March 2012,there are 553 patients with HCV Ab positive test visited the outpatient clinic in the gastroenterology &hepatology teaching hospital, had been taken into our study.

Every patient has been subjected to thorough history taking and clinical Examination ,the history was concentrating on the following points :

- Risk factors for infection (blood transfusion,surgery, etc) .
- House hold contact with the same disease
- Any symptom of liver disease (jaundice,subcostal discomfort , fatigue , etc) .
- Full clinical examination was done for every patient .
- Liver function test data;total serum bilirubin(TSB),aspartate aminotransferase (AST) , alanin aminotransferase (ALT) were measured .
- pT,INR .
- Serum protein,serum Albumin .

HCVAb positive assayed by third generation enzyme linked immune sorbant assay ELISA type III

- Investigations to exclude other causes of liver] disease (HBsAg , immune screen , etc) .
- Abdomen ultrasound was performed for all patients by experienced sonographist , the liver size , texture , the size of spleen and presence or absence of ascites was recorded .
- Alpha fetoprotein in patients with evidence of liver cirrhosis .
- Viral load using b-DNA-technology assay(bayer system340b-DNA3.0 analyzer)with detection limit 625-17857100 iu/ml .
- All patients assessd for Genotype using PCR & depend on two private laboratories .
- Liver biopsy was done in indicated cases those genotype 1or4 and those who has normal liver function tests and normal U/S after taking signed patient consent and there is no contraindication to procedure .

Among those patients only 90 patients where completed their work up and entered the their treatment phase according to schedule .

Statistical analysis:

All data were coded and enter to the computer by using statistical Package for Social Science (SPSS 14) association between variables. Measured by using Chi-Square test $P<0.05$ consider as level of significancy.

Results:

During the duration of study 553 patients with HCV Ab positive test visiting the outpatient clinic in Gastroenterologyand hepatology hospital Most of our patients discovered accidently during blood donation , testing before intervention , testing for life health insurance , high risk group ; medical staff ,and

household contact .

table 190 patients have completed treatment , 66 (73.3%) patients were male,24(26.7%) patients were female were included in study.

Age range was between 18-63years, mean age of patients is 41.4year , most of the patients lie in the young and middle age group range. Abnormal liver enzymes were seen in 20 patients(22.2%) of 90 patients .

table 2\

According to viral load patients divided into two groups, Only 27(30%)patients have viral load >600000U\ml while 63(70%)Patients have viral load<600000U\ml.39(42.2%) patients have been subjected to liver biopsy including those genotype 1or4 and those with normal liver function tests and normal U/S .

Table 3

80(88.9%%) patients have early virological response (EVR) 11(13.75%ofEVR patients) have partial early virological response (pEVR),69(76.2%) patients have complete early virological response (cEVR) .10 patients have no early virological response (<2log decreasein viral load) but we choosed to continue treatment as they have high viral load,increase in liver enzymes , 2 of them have progressive liver disease in histopathology .

Only 34(37.7%)patients who completed treatment achieved end treatment response (ETVR) .

Table (1)
How the patients diagnosed

Blood donation	37(41.1%)
Accidental & health life ensurance	22(24.5%)
Screening before surgery	16(17.8%)
Symptomatic	7(7.8%)
House hold contact	4(4.4%)
Before cardiac cathetre	4(4.4%)

Table (2)
Distribution of liver enzymes

Liver enzymes	NO %
=40 IU/ml	20(22.2)
<40 IU/ml	70(77.8)

Normalvalue<40iu/ml

Table (3)
Distribution of liver biopsy stages in the study

Liver biopsy	No
1	1
2	10
3	18
4	7
5	2
6	1
Total	39

Table (4)
Relation between viral load and liver enzymes

Liver enzymes	<600000 iu/ml	>600000iu/ml	Total
<40iu/ml	53(84.1%)	17(63%)	70(77.8%)
>40iu/ml	10(15.9%)	10(37%)	20(22.2%)
Total	63	27	90

P0.028

Discusion:

The program arranged by ministry of health by screening every patient before any intervention procedure lead to increase the number of cases seen in our health institute, however ,the overall prevalence in our country is still 0.3%[34].
Most of the patients discovered to be HCV Ab +ve during routine screening before elective surgery or interventional medicine , or during blood donation or screening of the family of infected persons or screening patient with chronic renal failure on hemodialysis[1].For this reason we have to emphasize the importance of screening of at risk individuals and the importance of making the test easily accessible for the population[8-13].
Most patients enrolled in our study were male66(73.3%) compared to 24 (26.7%) patients

were female,this what was found in other study[35] the explanation for this difference between male and female can be referred to that in our community less women subjected to screening test for HCV Ab compared to male and most of the blood donors are among male gender Male gender is associated with more rapid progression to cirrhosis and HCC[35]. The reason for this association is not clear, and hormonal effects on fibrogenesis have been suggested. Estrogen inhibits proliferation and activation of hepatic stellate cells in vitro. In addition, fibrosis appears to accelerate in postmenopausal women[36]

Age range of our study was between 18-63years, Mean age of patients was 41.4year ,most of the patients lie in the young and middle age group range.Most of our patients had low viral load (less than 600000 iu/ml in 63patient(70%) while 27 patients (30%) had viral load >600000iu/ml There was no significant correlation between pretreatment viral load and the age of the patients at presentation,this is the condition found in other study[37]. there was better end treatment virological response when pretreatment viral load low, this relation confirmed statistically(p value<0.05) this consistent with other study[38] .Inthis study; there was a significant correlation between viral load and liver enzymes as shown in table (4),this what found in other study[39].

The most common genotype was 1 occuring in 50% of the patients followed by genotype 4 (36.7) this is similar to other study in our country [40]and similar to nearby area like turkey and Iran but different from other area like Syria[41]

Conclusion:

Most common presentations was incidental during blood donation or during screening before interventional medical procedure.Hepatitis C was more common among the male gender , most of our patient have low viral load <600000 iu/ml .

There was significant association between the viral load and liver enzymes but There was no correlation between pretreatment viral load neither to the age of the patient nor to the stage of liver fibrosis or genotype .The predominant genotype was 1 occur in 50% followed by genotype 4 .Most of our patients got early virologic response .

End treatment viralogical responsewass seen in only 37.78% which has significant association with genotype,early virological response .

Recommendation:

Attempts to improve adherence to therapy and the early detection together with treatment of complications are needed to achieve better response to therapy.

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