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EVALUATION OF DURABILITY OF SUSTAINED VIROLOGICAL RESPONSE (S.V.R.) IN CHRONIC HEPATITIS C TREATED PATIENTS

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ABSTRACT

Background: The introduction of direct acting anti virals hase increased sustained virological response (SVR) rates in chronic hepatitis C infection. At present, data on long-term durability of viral eradication after successful triple therapy are lacking.

Objective: The predicators of durability of Sustained Virological response (S.V.R.) and its impact as pre-treatment markers.

Patients and Methods: Sixty patients with chronic hepatitis C virus achieved S.V.R. (sustained virological response). After 12 months of treatment, all patients were subjected to D.M., H.T.N, any special habits like smoking, clinical examination, PCR for HCV, IL28B genotyping, Liver function tests, CBC and other associated diseases e.g. HIV ,HBV, Serum iorn concentration.

Results: Several factors (host or viral-related factors or treatment related factors) influenced response to therapy and durability of S.V.R, advanced fibrosis, cirrhosis and steatosis have a negative impact on S.V.R. Also, IL28B genotyping can influence the durability of S.V.R. Patients with CC genotype were more likely to be cured by Peg-IFN and RBV, or recent free INF therapy.

Conclusions: Many factors can influence patients response to therapy and durability of SVR and IL28B C/C genotype play a great role in clearance of HCV.

Key words: Sustained virological response, Chronic hepatitis, Virus C.

INTRODUCTION

Hepatitis C is an infectious disease affecting primarily the liver caused by the hepatitis C virus (HCV). The infection is often asymptomatic, but chronic infection can lead to scarring of the liver and ultimately to cirrhosis, which is generally apparent after many years. In some cases, those with cirrhosis will go on to develop liver failure, cancer liver or life-threatening esophageal and gastric varices**.**Chronic infection after several years may cause cirrhosis or cancer liver . Fatty changes to the liver occur in about half of those infected patients and are development of usually present before cirrhosis. **(Paradis and Bedossa, 2008).**

Several factors have been implicated in predicting the response to the treatment and it may be used as pretreatment markers for selection of the patient ***(Lee et al., 2011).***

Both host and viral factors can influence patient response to therapy & durability of (SVR) including age, sex, degree of activity, degree of liver fibrosis or cirrhosis, pretreatment viral load, type of interferon, genetic variation of $IL_{28}B$, HCV genotype, response pattern to previous antiviral therapy ***(Maylin et al., 2009).***

SVR is defined by the absence of detectable HCV RNA in the serum as shown by a qualitative HCV RNA assay with lower limit of detection of 15 Iu/mL or less at week 24 after the end of treatment ***(Shiratori et al., 2012)***.

SVR rates for genotype 1-infected patients ranged from 41%-52% after 48 weeks of PEG IFN / RBV and Interferon free therapy as opposed to 76%-84% in genotypes 2 and 3 ***(Hadziyannis et al., 2014)***.

Over the past years, interferon (IFN) free dosing regimens have become available to treat chronic hepatitis C. Offering high rates of sustained virological response (SVR), short treatment and improved tolerability, INF-free treatment represents the paradigm for both treatment-naive and exprienced patients**. (Zeuzem et al., 2014).**

The present work aimed to evaluate to S.V.R. and its impact as pre-treatment markers.

PATIENTS AND METHODS

Sixty patients with chronic hepatitis C virus achieved S.V.R. (sustained virological response) after 6 months of treatment completion were selected from patients admitted to Internal Medicine Department, **Kobri-El-Koba Military Hospital**.

All patients were subjected to careful and detailed history, thorough clinical examination, laboratory investigations including PCR,liver function test and CBC, other associated diseases, e.g. HIV, HBV, Serum iorn concentration, IL28B genotyping by sequencing mechanism to detect type of IL28B polymorphism, and Fibrotest to determine the severity of liver disease (degree of liver fibrosis and cirrhosis).

The patients were evaluated after 12 months from the end of treatment, and were classified into two equal groups.

Group (A) were -ve HCV RNA PCR with durable S.V.R. at 12 months after the end of treatment, and Group (B) were +ve HCV RNA PCR 12 months after the end of treatment.

RESULTS

A total of 60 patients (females were equal to males, age 59.6+6.8 years) with a sustained virological response (SVR) were evaluated. The SVR in smokers was significantly lower than in nonsmokers. There was a highly significant difference in IL28B genotyping. Percentage of CC genotype were high among group(A) than group (B). The percentage of CT genotype and TT genotype were high among group (B) than group(A)(Table 1).

Table (1): Characteristics of patients.

Groups / Parameters	Group (A)		Group (B)		P value
	Mean	**S.D**	**Mean**	**S.D**	
Age (years)	56.8	7.6	65.4	5.6	<0.001
	Number	**Percentage**	**Number**	**Percentage**	
Male	15	50.0%	16	53.3%	0.79
Female	15	50.0%	14	46.7%	
-ve Smoking	17	56.7%	16	53.3%	0.79
+ve	13	43.3	14	46.7	
IL28B CC	24	80.0	2	6.7	<0.001
IL28B CT	4	13.3	18	60.0	<0.001
IL28B TT	2	6.7	10	33.3	<0.001

There was a significant difference as regard associated diseases (D.M, H.T.N, D.M and H.T.N Hepatic steatosis) between the two studied groups of patients (Table 2).

Table (2): Comparison between the two studied groups of patients as regard different associated disease.

Groups / Parameters		Group (A)		Group (B)		P value
		Number	**Percentage**	**Number**	**Percentage**	
Some associated diseases	No D.M, No H.T.N	14	46.7	4	13.3	0.02 (S)
	D.M	9	30.0	9	30.0	
	H.T.N	5	16.7	7	23.3	
	D.M and H.T.N	2	6.7	7	23.3	
	Hepatic steatosis	0	0.0	3	10.0	

The difference in degree of disease severity (liver fibrosis) was highly significant (P value <0.01) between group (A) and group (B). The percentage of severity of liver fibrosis by (fibrotest) was high among group (B) than group (A) (Table 3).

Table (3): Comparison between the two studied groups of patients as regard disease severity

Groups / Parameters	Group (A)		Group (B)		P value
	Number	Percentage	Number	Percentage	
F0	6	20.0	0	0.0	0.001 (H.S)
F1	8	26.7	0	0.0	
F2	12	40.0	5	16.7	
F3	3	10.0	19	63.3	
F4	1	3.3	6	20.0	

There were highly significant difference between group (A) and group (B) as regard pretreatment viral load The range of pretreatment viral load was high among group (B) than group (A) (Table 4).

Table (4): Comparison between the two studied groups of patients as regard the pretreatment viral load.

	Median viral load (range)	MW	P value
Group (A)	1.000.000 (11.628 - 4.000.000)	33.6	<0.001 (H.S)
Group (B)	4.273.000 (900.312 - 10.916.000)		

DISCUSSION

This study con?rms that SVR equals permanent HCV eradication by whatever interferon-based anti-viral treatment it was achieved. Our data indicate that the Favourable long-term outcome reported after peg-interferon/ ribavirin combination therapy seems to hold true for patients treated with a triple therapy with peg-interferon/ ribavirin in combination with a direct anti-viral agent. To the best of our knowledge, this is the study reporting long-term virological outcomes in patients with hepatitis C after successful anti-viral triple therapy **. (De Marcol et al ., 2012).**

There are the oretical concerns regarding the durability of HCV eradication after successful direct-acting anti viral-based triple therapy. During direct-acting anti-viral treatment resistance-associated variants with reduced rep-lication ?tness compared with the wild type virus may emerge. If these resistance-associated variants cannot be eliminated by the required peginterferon/ribavirin backbone, strains with reduced replication ?tness may persist in low concentration and

may account for late relapses **(Nelson DR et al., 2012).**

In our study, 30 patients with a sustained virological response (SVR24) experienced a relapse 12 months later. Both patients completed a full course of anti-viral treatment without dose modi?cations or discontinuations of medications with peg-interferon/ ribavirin and free- interferon therapy . The serum samples of both patients (taken at base line and after relapse) revealed no viral resistance and showed viral homology to samples collected at screening. the relapsed patients showed a risk behavior regarding HCV infection before reappearance of HCV.

Thus, in patients a late relapse rather than a newly acquired infection seems to be the reason for reappearance of hepatitis C virus. Obviously, an ongoing occult HCV infection cannot be excluded with certainty **(De Marcol et al., 2012).**

Overall, our data show that it seems appropriate to extrapolate the encouraging long-term data of dual combination therapy to triple therapy with direct-acting ant virals. The laterel apserate was 1.9% (95%CI:0.24–6.8) as compared to 0.18% (0.004-1.01) in a much larger cohort of patients with SVR after dual therapy. As all patients treated with direct-acting anti-viral in combination with PEGIFN/RBV achieving similar rates of SVR were followed prospectively, a potential selection bias is unlikely**.(Ruller et al., 2013).**

However, in parallel to reported late relapses after successful dual therapy, late relapses after triple therapy although a rare event - seem to occur within the ?rst months after SVR like in the cases in our cohort .The fact that both relapses were observed in patients receiving free-interferon therapy occurred possibly just by chance, as the mode of action and the ef?cacy of the protease inhibitors are similar. Never theless, it seems advisable to con?rm a successful HCV eradication within the ?rst year of follow-up after achieving a sustained virological response. From our data , no impact on the durability of SVR after interferon- free treatments can be inferred.**(Lawitz EPF et al., 2012).**

CONCLUSION

Our study shows that HCV eradication by triple therapy remains durable and con?rms an excellent long-term prognosis of HCV patients with SVR. To assess the long-term clinical bene?t of triple therapy, studies with a longer follow-up and larger patient numbers are needed. And that there are several factors related to the virus and patient releated factors can affect the patients treatment response and durability of SVR. It was clear from the study that the full advanced fibrosis and cirrhosis have a negative effect on the response of viral steady. And that the genetic factor for IL28B has an effect on SVR. And patients who have genotype cc were the most responsive to treatment.

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تقييم متانة الاستجابة الفيروسية المطردة في مرضى الالتهاب الكبدي المزمن (سى) ما بعد العلاج

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تبين دراستنا إن القضاء علي فيروس سي عن طريق العلاج الثلاثى يبقي دائم علي المدي الطويل وتتحقق فيه مدي الاستجابة الفيروسية المطردة . ولتقييم الفائدة المستديمة للعلاج الثلاثى نحتاج لإجراء دراسات اطول علي اعداد اكبر من المرضي. وان هناك عدة عوامل ذات صله بالفيروس والمريض وعوامل مرتبطة بالعلاج يمكن ان تؤثر علي استجابة المريض للعلاج ومتانة الاستجابة الفيروسيه المطردة. واتضح من الدراسة ان التليف المتقدم والتليف الكامل والتشمع لهم تأثير سلبي واضح علي الاستجابة الفيروسية المطردة. وان العامل الوراثي لIL28B له تأثير عل الاستجابة الفيروسية المستمرة. وإن المرضي الذين يملكون النمط الجيني CC هم اكثر استجابة للعلاج.