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TH1 VERSUS TH17 IN CHRONIC HEPATITIS C VIRUS INFECTION

By

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ABSTRACT

Background: Hepatitis C virus (HCV) is a major cause of chronic liver disease affecting close to 170 million people worldwide. Egypt Demographic Health Surveys (EDHS) measured antibody prevalence among adult population aged 15-59 years at 14.7% in 2009 and at 10.0% in 2015. Approximately, 85% of patients acutely infected with HCV progress to chronic liver disease with persistence of HCV RNA for more than 6 months. Among patients with chronic HCV infection, 15-20% progress to end-stage liver disease and approximately 14% of these patients progress to cirrhosis or hepatocellular carcinoma with time. With hepatitis C, being a national care problem, predicting the outcome of treatment in these patients becomes very important.

Objectives: The aim of this study was to evaluate and predict the response in hepatitis C virus patients to pegylated interferon alpha and ribavirin therapy in association with estimation of the percentage of TH1 and TH17 by flowcytometry.

Patients and Methods: This study was conducted on 50 patients with proven chronic hepatitis C virus infection based on by PCR technique and histopathology (25 responders and 25 non-responders). All of them were treated by combined pegylated interferon alfa plus ribavirin orally. Patients with history of previous interferon therapy, evidence of other systemic illness including: (hepatic, renal, cardiac, diabetic and neoplastic disease), chronic inflammatory disease, unstable thyroid dysfunction, unstable psychiatric disorder or history of any organ transplantation were excluded. All patients were F2or F3 on fibroscan. By flowcytometry, human CD4 percentage was estimated by using fluorescein-conjugated antibody. Human TH17 percentage was estimated by using PerCP-conjugated antibody, and TH1 was estimated by phycoerythron conjugated antibody. Both TH1 and TH17 were performed at weeks 0 and retested again after 12 weeks.

Results: After 12 weeks from starting of therapy, there was an increase in percentage of TH1 in non-responders of therapy compared to responders with no difference in the percentage of TH17 between the two groups.

Conclusion: There was a positive correlation between TH1 and TH17 in both groups before and after therapy. Also, we found that 98% of patients achieved sustained virological response 12 weeks after completion of therapy (SVR_{12}) showed sustained virological response 24 weeks after completion of therapy (SVR_{24}).

Key words: Hepatitis C virus, immunological response, TH1, TH17, IFN, causes of resistance.

INTRODUCTION

Hepatitis C virus (HCV) is a global health problem characterized by persistent infection, limited therapeutic options, poor treatment responses, and no available vaccine. Following years of intensive research into the pathogenesis of HCV, it has become evident that this virus is able to modulate host immunity, in particular T cell responses and by doing so facilitates chronic infection. The mechanisms by which HCV impairs antiviral T cell immunity include blunted T cell activation and proliferation by up-regulating inhibitory pathways, skewed T cell differentiation (Th1 deficiency or Th2 dominance), T cell anergy (antigen-specific hypo-responsiveness or exhaustion), T cell depletion (cell apoptosis or death), and induction of regulatory T cells *(Xiao et al., 2013).*

T helper (Th17) cells are a discovered TH cell subset with implications in both host defense and autoimmunity. Th17 implications in chronic HCV infection are not well characterized. Given the important role in multiple other immune and inflammatory conditions, they are of obvious interest. Specific HCV-Th17 cells are implicated in immune response modulation, correlated with fibrosis severity and intrahepatic inflammatory status. Serum IL-17 levels are higher in chronic HCV infected patients and Th17 cytokines are modulated within the therapeutic response at anti-viral treatment. However, intriguing data indicate that Th17 could be associated with spontaneous HCV clearance. It is possible that Th17 could play a dual role (both beneficial and harmful) and that an unbalance of regulating factors (chemokines, transcription factors, receptor expression, etc.) rather than the lymphocyte itself could tip the Th17 immune response one way or another *(Baianescu et al., 2012).*

Early detection of non-responders and continuing treatment for patients who are more likely to respond is of major importance in improving the outcome of patients with chronic HCV infection. Hence, accurate prediction of treatment response after 12 weeks of therapy associated with immunogenic role of proinflammatory T cells (TH1 & TH17) have become a major factor in the management algorithm for chronic HCV infection *(Navaneethan et al., 2009).*

The aim of the present work was to evaluate and predict the response in hepatitis C virus patients to pegylated interferon alpha and ribavirin therapy in association with estimation of the percentageof TH1 and TH17 by flowcytometry.

PATIENTS AND METHODS

This control study was conducted in Al-Hussein hospital throughout the period between June 2014 and June 2016. Patients enrolled in the current study were consecutively enrolled from Al-Qahera El-Fatmia hospital. This study was conducted on 50 patients with proven chronic hepatitis C virus infection based on by PCR technique and histopathology. All patients were F2 and F3 on liver biopsy. *They were 2 groups of patients:*

Group I (25 patients) showed SVR_{12} (HCV RNA below detection limit after 12 weeks of treatment).

Group II (25 patients) did not respond to treatment after 12 weeks of treatment.

Both groups were treated weekly by pegylated interferon alpha 180ugm, in addition to weight-based Ribavirin daily for 12 weeks.

Inclusion criteria: Adult patients aged 25 to 55 years with documented chronic HCV infection.

Exclusion criteria: Pregnancy or breast-feeding females, history of previous interferon therapy, evidence of other systemic illness including hepatic, renal, cardiac, diabetic and neoplastic disease, chronic inflammatory disease, unstable thyroid dysfunction, unstable psychiatric disorder, or history of any organ transplantation.

An informed consent was obtained from all participants before recruitment in the study and before any invasive procedure. Approvals of all the concerned authorities were obtained.

For all patients, the following were done:

A full medical history including age, sex, history of schistosomiasis or viral hepatitis, exposure to high risk factors, history suggestive of liver cell failure or other disorders, e.g. D.M., and also any special habits like smoking or alcohol intake.

Thorough clinical examination for assessment BMI and examination of the abdomen (Liver size and consistency, spleen and ascites).

Assessing of fibrosis stage was done through FIB-4 calculation.

Fibroscan and Liver biopsy.

The following Laboratory tests were done before and after 12 weeks of treatment:

Complete blood picture (Sysmex KX-21N-Japan), ALT&AST (Randox u.v. method- United Kingdom), total bilirubin, s.albumin and s.creatinine (Randox Colorimetric method- United Kingdom), prothrombin time and INR (Sysmex CA-600-Japan), quantitative PCR (ThermoScientific, Germany, Lot 00459337), ANA, HBsAg, HIV (BIO-RAD Elisa- USA), TSH and AFP (Cobas 6000-Germany), TH1 and TH17 by flowcytometry (R&D SYSTEMS - USA).

Specimen collection:

10 ml of venous blood were withdrawn from all subjects by venipuncture under complete aseptic condition and divided into multiple tubes each with suitable anticoagulants for estimation of CBC, PT, blood chemistry and also TH1, Th17 by flowcytometry.

Statistical methods: Data analysis were performed using IBM SPSS statistics software version 22.0, IBM Corp., Chicago, USA, 2013. Descriptive statistics were done for quantitative data as minimum and maximum of the range as well as mean ± SD (standard deviation) for quantitative normally distributed data, while it was done for qualitative data as number and percentage. Inferential analyses were done for paired t-test in cases of two dependent groups with normally distributed data. Correlations were done using Pearson correlation for numerical normally distributed data. Logistic regression model was used to find out independent factors affecting response. The level of significance was taken at P value ≤ 0.05.

RESULTS

Among non-responders, TH1 significantly increased after treatment **(Table 1).**

Table (1): Laboratory findings before and after treatment among responders and non-responders

Variable			Before	After	P
TH1 %	Responders	Mean±SD	40.8±16.8	41.1±19.4	0.952
		Range	4.1–63.8	10.5–79.0	
	Non-responders	Mean±SD	44.6±14.1	53.8±16.1	0.010*
		Range	15.7–71.4	22.7–84.0	
TH17 %	Responders	Mean±SD	13.5±10.1	13.3±8.5	0.937
		Range	0.1–39.8	1.0–30.4	
	Non-responders	Mean±SD	17.8±10.7	17.9±9.1	0.974
		Range	3.3–39.8	4.7–34.4	
HCV RNA ($x10^6$/ml)	Responders	Mean±SD	2.0±2.6	0.0±0.0	<0.001*
		Range	0.1–9.6	0.0-0.0	
	Non-responders	Mean±SD	1.2±1.9	0.7±1.0	0.283
		Range	0.1–8.1	0.1–4.4	

There was significant positive correlation between TH1 and TH17 before treatment among both responders and non-responders **(Table 2).**

Table (2): Correlations between laboratory findings before treatment among responders and non-responders.

Variables		Measure	TH1%	TH17%
TH17 %	Responders	r	0.772	-
		p	<0.001*	-
	Non-responders	r	0.756	-
		p	<0.001*	-
Fib4	Responders	r	-0.063	0.095
		p	0.766	0.651
	Non-responders	r	-0.139	-0.161
		p	0.507	0.443

There was significant positive correlation between TH1 and TH17 before treatment among both responders and non-responders **(Table 3).**

Table (3): Correlations between TH1, TH 17 and laboratory findings after treatment among responders and non-responders.

Variables		Measure	TH1%	TH17%
TH17 %	Responders	r	0.773	-
		p	<0.001*	-
	Non-responders	r	0.734	-
		p	<0.001*	-
AFP (ng/ml)	Responders	r	0.547	0.047
		p	0.688	0.077
	Non-responders	r	0.212	0.062
		p	0.309	0.770

Different variables had no significant diagnostic performance in predicting responding condition after treatment and there was no statistical significant difference among responders and non-responders according to radiological findings before treatment **(Table 4)**.

Table (4): Diagnostic performance of different variables in predicting responding condition after treatment.

Variables	AUC	SE	P	95% CI
AFP (ng/ml)	0.505	0.084	0.954	0.500–0.670
HCV RNA (x106/ml)	0.656	0.078	0.059	0.502–0.810
Fib4	0.512	0.084	0.884	0.500–0.676
TH1 %	0.547	0.082	0.567	0.500–0.709
TH17 %	0.604	0.081	0.207	0.500–0.762

98% of patients achieved SVR_{12} showed SVR_{24}.

DISCUSSION

Our target was to fix most of the predictor factors as possible between responders and non-responders to identify some cellular immunological markers associated with SVR as prestep to modulate immune response in that direction to improve clinical management *(Navaneethan et al, 2009)*. The cellular immune response against HCV is induced in acute HCV infection by NK cells while in chronic stage by CD8 cytotoxic T cells

mainly. Both effector subsets and regulatory lymphocytes are found in the liver of chronic HCV, and the balance of the cells recruited will determine the severity of the liver disease. The pathogenesis of chronic HCV disease which lead to liver damage is suggested to be due to dysregulated immune response with exaggerated proinflammatory cytokines released mainly by TH1 and TH17 compared to anti-inflammatory cytokines released from Th2 and Treg. *(Balanescu et al., 2012).*

It is documented that TH17 and TH1 cells are developmentally related. Furthermore, *Romagnani., 2008* observed the presence in the circulation TH cells that can produce IL-17 and IFN-gamma as well as the flexibility of human TH17 clones to produce IFN- gamma in addition to IL-17 in response to IL-12. *MacDonald et al., 2002* stated that specific TH17 and TH1 cells are induced against the core protein in HCV infection. Additionally, to its potent proinflammatory capacity, IL-17 exerts its effects through facilitating T cell infiltration, activation and amplification of the immune response by inducing production of IL-6. In addition, IL-17 synergizes with other cytokines, in particular with IL-1β and tumor necrosis factor (TNF)-α *(Balanescu et al., 2012).*

Interferon-gamma (IFN-γ), as one of the TH1 related cytokine, has elicited great interest in chronic viral infections because it is abundantly produced and has direct antiviral activity. The pathogenesis of viral chronic liver disease that leads to liver damage is suggested to be immune-mediated *(Barakat et al., 2012).* It has been shown that patients with chronic hepatitis C virus (HCV) infection display a polarized NK cell phenotype with IFN-γ production and that kinetics of NK, with IFN gamma production, to alpha IFN therapy will be important in HCV management *(Ahlenstiel et al., 2010).*

In our results, before treatment there was no difference in TH1 percentage between responders and non-responders. 12 weeks after treatment with pegylated IFN and ribavirin, TH1 cells level were higher in non-responders compared to responders. This is going with studies done by *Jimenez-Sousa et al., (2010), Fathy et al., (2011) and Lu et al., (2016)* who observed that patients of HCV under pegylated IFN and Ribavirin therapy with increased IFN-gamma failed to achieve RVR compared to HCV patients with decreased IFN-gamma levels. The refractory effect to exogenous alpha IFN may be attributed to direct effect of excess endogenous alpha IFN through induction of intracellular suppression factors, e.g. suppressor of cytokine signalling 3 (SOCS3) as homeostatic mechanism at cellular level.

The variation in TH1 activity could be attributed to drug effect. In chronic hepatitis C patients who were treated by pegylated IFN and ribavirin showed marked decreased activity of TH1 (expression of gamma IFN) which is not secondary to reduction of viral load since no correlation was found between HCV RNA and IFN gamma level but it was mediated by Ribavirin as no modification of IFN gamma expression was seen in patients treated with alpha IFN alone and there was no modulation of IL2, IL4, IL10 expression found in patients treated with INF alone or in combination with ribavirin *(Bergamini et al., 2009).* This variation in

TH1 activity could be attributed to viral effect. Hepatitis C induces immuno-suppressive cytokines IL-10 and TGF-B, which are able to inhibit TH17, TH1 and inhibition of intrahepatic IFN-gamma production by HCV NS5A *(Kanda et al., 2009).* In addition, defective IFN- gamma production by peripheral blood mononuclear cells was observed in HCV-infected patients in response to nonstructural protein 4 *(Fathy et al., 2011).* It has been observed that HCV NS3-specific T cells do not proliferate during treatment of chronic HCV infection with ribavirin in combination with IFN-a and proliferated after stopping of treatment *(Bergamini et al., 2009).* in addition, the variation of TH1 activity could be due to tolerogenic effect of liver tissue. In chronic HCV infection a weak CD4+/CD8+ T cell response is observed. The tolerogenic potential of the liver, may be caused by either a primary T cell failure in which the dendritic cells fail to stimulate the antigen-specific T cells, or T cell exhaustion in which virus-specific T cells become depleted by a continuous high viral load *(Fathy et al., 2011).*

Contradictory studies done by *Barakat et al. (2012)* who found increase in IFN gamma level in responders compared to non-responders with significant correlations between IFN and HCV viral load as assessed by PCR as well as liver condition which assessed by high ALT. In vitro and in murine models, ribavirin may prime human T cell for an increased production of TH1 cytokines, such as IFN-g and IL-2, which play a key role in antiviral responses. On the basis of these findings it has been suggested that ribavirin may potentiate IFN-a activity against HCV by immune-mediated mechanisms. The capacity of ribavirin to potentiate the anti-HCV effect of IFN-a is better explained by its ability to increase up to 6´1 fold the intracellular levels of the bioactive enzyme 2',50-oligoadenylatesynthetase, which mediates most of the antiviral effects of IFN-a, with respect to the levels obtained by IFN-a alone *(Martin et al., 1998).*

Increased circulating TH17 and intrahepatic HCV-specific TH17 cells were observed in chronic HCV patients. HCV-specific TH17 cells were correlated with severity of liver inflammation in chronic HCV patients and positively correlated with ALT, but not with viral load. Serum IL-17 levels were higher in chronic HCV patients when compared to controls. However, no association was found between serum IL-17 concentration, ALT levels and viral load *(Chang et al., 2012).* Another study showed that IL-17A, IL-17F, and IL-22 are produced by CD4+ and CD8+T cells at significantly higher levels within the liver as compared to peripheral blood. A greater proportion of intra-hepatic lymphocytes co-secreted IL-22 along with IL-17 than in the peripheral blood. The roles of IL-17 and IL-22 are not completely understood, but the higher co-expression of IL-22 may function as a feedback that diminishes IL-17-mediated inflammation (*Foster et al., 2012*).

In our study we did not find difference in the percentage of TH17 between responders and non-responders before and after treatment. Also, there was positive correlation between TH1 and TH17 in responders and non-responders before and after 12 weeks of therapy by pegylated interferon and ribavirin. This is going with study done by *Hao et al. (2014)* who

observed that the percentage of TH17 cells and IL-17, IL-22 and IL-23 concentrations did not change during therapy in either responder or non-responder. On the contrary study done by *Balanescu et al. (2012)* found that IL-17 levels were elevated in the serum of chronic HCV patients and values did not correlate with viral loads following 12 weeks of treatment with IFN-α and ribavirin and that the increase in IL17 levels could also play a part in hepatic viral persistence by means of antiapoptotic molecules upregulation. IFN-γ showed significant reduction after 12 weeks of treatment in contrast to IL-17 serum levels and no difference was observed between responders and non-responders. *Kim et al. (2009)* observed that the increase in TH17 could be attributed to HCV effect. HCV proteins modify the differentiation of peripheral monocytes into mature dendritic cells (DC)s. HCV core protein and NS3 protein interfere with the process of DCs maturation. During in vitro differentiation of monocytes into DCs, the presence of either core or NS3 protein caused down-regulation of CD1a and CD1b and these effects were dose-dependent. These two proteins could be engaged in a form of immune subversion, impairing the normal differentiation of DCs *(Tu et al., 2012).* This abnormal DC differentiation determined a skew towards TH17 cell subset differentiation that might be implicated in liver injury related to the viral infection. Other studies found that serum IL17 cytokine was reduced after 12 weeks of therapy and responders showed greater cytokine decline. This may be attributed to reciprocal increase in Treg as there is plasticity between Treg and TH17, so It is possible that TH17 could play a dual role and not TH17 itself, but a misbalance of its regulating factors (chemokines, transcription factors, receptor expression, etc.) could direct TH17in one way or another *(Balanescu et al., 2012).* Also, we found that 98% of patients achieved sustained virological response 12 weeks after completion of therapy (SVR_{12}) showed sustained virological response 24 weeks after completion of therapy (SVR_{24}), this is going with studies done by *Burgess et al. (2016).*

CONCLUSION

There was an increase in percentage of TH1 in non-responders of therapy (pegylated interferon alpha and ribavirin) after 12 weeks from starting of therapy compared to responders with no difference in the percentage of TH17 between the two groups , and there was a positive correlation between TH1 and TH17 in both groups before and after therapy. 98% of patients achieved SVR_{12} showed SVR_{24}. We recommend extended studies to explore the immunological role of proinflammatory T cells (TH1 and TH17) associated with SVR_{12} to improve the clinical management.

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الخلايا المساعدة تى١ مقابل خلايا تى١٧ فى فيروس الإلتهاب الكبدى الوبائي سى

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خلفية البحث : فيروس الالتهاب الكبدي الوبائي سى هو أحد الأسباب الرئيسية لأمراض الكبد المزمنة التي تصيب ما يقرب من ١٧٠ مليون شخص في جميع أنحاء العالم. و فى قياس المسوح الصحية الديموغرافية في مصر كانت نسبه انتشار الأجسام المضادة بين السكان البالغين الذين تتراوح أعمارهم بين ١٥-٥٩ سنة في ١٤,٧ ٪ في عام ٢٠٠٩ و ١٠,٠ ٪ في عام ٢٠١٥. يتحول ما يقرب من ٨٥ ٪ من المرضى المصابين بشدة مع تقدم الالتهاب الكبدي الوبائي إلى مرض الكبد المزمن مع استمرار حمض النووي الريبيلفيروس الالتهاب الكبدى الوبائي الى أكثر من ٦ أشهر. بين المرضى الذين يعانون من عدوى فيروس التهاب الكبد الوبائي المزمن ،يتحول ١٥-٢٠ ٪ إلى المرحلة الأخيرة من المرض ونحو ١٤ ٪ من هؤلاء المرضى سيتطور إلى تليف الكبد أو سرطان الكبد مع مرور الوقت. مع كون التهاب الكبد C مشكلة رعاية وطنية ، فإن التنبؤ بنتائج العلاج في هؤلاء المرضى يصبح مهمًا جدًا.

الهدف من البحث: الهدف من هذه الدراسة هو تقييم وتوقع الاستجابة في مرضى فيروس التهاب الكبد الوبائي إلى مضاد للفيروسات ألفا وعلاج ريبافيرين بالاشتراك مع تقدير النسبة الخلايا الليمفاوية المساعدة تى1 و الخلايا الليمفاوية المساعدة تى17 بواسطة قياس التدفق الخلوي.

المرضى وطرق البحث: أجريت هذه الدراسة على ٥٠ مريضًا مصابًا بعدوى فيروس التهاب الكبد المزمن المؤكدة استنادًا إلى تقنية تفاعل البلمرة المتسلسل والتشريح المرضي (٢٥ مستجيبًا و ٢٥ مستجيباً). تم علاج كل منهم عن طريق الجمع بين مضاد للفيروسات ألفا بالإضافة إلى ريبافيرين شفويا. تم استبعاد المرضى الذين لديهم تاريخ سابق من علاج مضاد للفيروسات، وجود أمراض جهازية أخرى بما في ذلك: (الكبد، الكلى، أمراض القلب، مرض السكري والأورام) ، مرض التهابي مزمن ، عدم استقرار الغدة الدرقية ، اضطراب نفسي غير مستقر أو تاريخ أي زرع عضو. كان جميع المرضىF3or F3 على فيبروسكان بواسطة التدفق الخلوي ، تم تقدير نسبة CD4 البشرية باستخدام الأجسام المضادةالمترافقبالفلوريسين ، وقدرت نسبة الخلايا الليمفاويه المساعدة تى17باستخدام الأجسام المضادة المترافقه للبر سي بي و تم تقدير الخلايا الليمفاوية المساعدة تى1 بواسطة الأجسام

المضادة المترافقة فيكوايريثرون. تم إجراء كل من الخلايا الليمفاوية المساعدة تى1 والخلايا الليمفاوية المساعدة تى17 في الأسبوع وإعادة اختبارها مرة أخرى بعد ١٢ أسبوعًا.

النتائج: بعد ١٢ أسبوعا من بدء العلاج كان هناك زيادة في نسبة الخلايا الليمفاوية المساعدة تى1 في غير المستجيبين للعلاج مقارنة مع المستجيبين كا انه لا يوجد فرق في نسبة الخلايا الليمفاوية المساعدة تى17 في بين المجموعتين.

الاستنتاج: كان هناك ارتباطاً إيجابياً بين الخلايا الليمفاوية المساعدة تى1 و الخلايا الليمفاوية المساعدة تى17 في كلا المجموعتين قبل وبعد العلاج أيضا ، وقد وجدنا أن ٩٨ ٪ من المرضى حصلوا على إستجابة فيروسية مستمرة بعد ١٢ أسبوعًا من إنتهاء العلاج ، وأظهروا إستجابة فيروسية مستمرة بعد ٢٤ أسبوعًا من إنتهاء العلاج.