Journal Homepage: -www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/2808
DOI URL: http://dx.doi.org/10.21474/IJAR01/2808

RESEARCH ARTICLE

The Effect of Interferon/Ribavirin Therapy on the Levels of Angiopoetin-2 andTIE-2 in Chronic Hepatitis C Patients.

Gamal Esmat[1], Khalil A. Khalil[2], Mohamed Abdou[2], Fadia Mustafa[3], Ayman Salem[2], Mahmoud Shedid[4], and Mohamed Mosaad[4,5].

1. Department of Tropical Medicine and Hepatology, Cairo University, Cairo, Egypt.
2. Department of Internal Medicine, Faculty of Medicine, Suez Canal University, Ismailia, Egypt.
3. Department of Clinical Pathology, Faculty of Medicine, Suez Canal University, Ismailia, Egypt.
4. Department of Endemic and Infectious diseases, Faculty of Medicine, Suez Canal University, Ismailia, Egypt.
5. Department of Internal Medicine, Taibah University, Medina, Saudi Arabia.

Manuscript Info

Manuscript History

Received: 15 November 2016
Final Accepted: 17 December 2016
Published: January 2017

Key words:-
Angiopoetin -2, Hepatitis C, Interferon therapy, Tie-2.

Abstract

Aim: to identify the effect of hepatitis C virus treatment by pegylated interferon and ribavirin on the level of angiogenic factor (Angiopoetin -2 and its receptor Tie-2) and detection of their levels as a predictor of response to treatment**.**

Methods: one hundredand sixteen patients with chronic hepatitis C, who were candidate for interferon and ribavirin combination therapy according to the Egyptian Ministry of Health Program, enrolled in this study where the levels ofAngiopoetin -2 and its receptor Tie-2were determinedbefore and after the combination therapy.

Results: There was a significant decline of serum Ang-2 after the end of treatment, week 48 (330.8 ± 73.0) compared to the baseline values (544.7 ± 64.1) in all patients (P<0.0 1),while There was a significant increase of serum sTie-2after the end of treatment, week 48 (31.2 ± 1.04) compared to the baseline values (17.7 ± 2.1) in all patients (P<0.0 1). However there was no difference between responders (212.5 ± 87.1) and non-responders (228.3 ± 22.9) at week 48 regarding serum Ang-2, and also there was no difference between responders (13.4 ± 2.4) and non-responders (14.22 ± 2.39) at week 48 regarding serum Tie-2(P<0.0 1).

Conclusion: Angiopoetin -2 and its receptor Tie-2 may not be a useful predictors for treatment responses to pegylated interferon and ribavirin.

Copy Right, IJAR, 2016,. All rights reserved.

Introduction:-

About 3% of the world's population is infected with HCV, mostly found in the developing countries, while the prevalence ranging from 0.1–5% in different European countries [(1)].Egypt has the largest epidemic of hepatitis C virus (HCV) in the world; the released Egyptian Demographic Health Survey [EDHS] tested a representative sample of the entire country for HCV antibody where over 11,000 individuals were tested, the sample included both urban and rural populations and included all 27 governorates of Egypt, The overall prevalence positive for antibody to HCV was 14.7%[(2)]. Unfortunately, most of the patients with HCV infection will progress to chronic liver diseases

Corresponding Author:-Mohamed Mosaad.
Address:-Department of Tropical Medicine Suez Canal University, Ismailia, Egypt.

(CLDs), liver cirrhosis and a respectable significant ratio will have hepatocellular carcinoma (HCC)[3-4]. Several mechanisms were identified in the pathogenesis of CLDs, the formation of new blood vessels is a key mechanism, where neovascularization and establishment of an abnormal angioarchitecture are related to its pathological progression [5]; moreover, the pathophysiology of portal hypertension is linked to an increased hepatic and splanchnic neovascularization[6], nevertheless, angiogenesis is a pivotal factor in the pathophysiology of HCC[7]. As suggested by Yoshiji et al., 2003[8], the close relationship between the progression of CLDs and angiogenesis brings about two potential clinical goals, first the detection of selected pro-angiogenic molecules that may serve as a non-invasive way to monitor both disease progression, as well as therapeutic response; second, anti-angiogenic therapy may be an effective tool for blocking or slowing down fibrogenic progression of CLDs. Although the recent advances in treatment of HCV, interferon and ribavirin combination therapy still the essential therapy in Egypt due to various reasons. The high prevalence of HCV in Egypt, progression of the disease to chronicity and liver cirrhosis which may be complicated by hepatocellular carcinoma, and the role of angiogenesis factors in the pathogenesis, motivated us to study the effect of Interferon/Ribavirin therapy on angiogenesis marker (Angiopoetin-2 and its receptor TIE-2) in chronic hepatitis C patients, and if we can use its pre-treatment level as a predictor of response to therapy or not?

Aim of the work:-

The aim of this work was to identify the effect of hepatitis C virus treatment by pegylated interferon and ribavirin on the level of angiogenic factor (Angiopoetin -2 and its receptor Tie-2) and detection of their levels as a predictor of response to treatment if any.

Subjects and Methods:-

A prospective study was conducted among one hundred and sixteen (116) patients at the center for treatment of viral hepatitis in Ismailia fever Hospital, Egypt, in the period from November, 2011 to December, 2013. All the patients have chronic liver disease due to HCV infection, and were candidate for interferon and ribavirin combination therapy according to the Egyptian Ministry of Health Program. Besides, the known exclusion criteria for the drugs contraindications and hypersensitivity, patients with co-infection with hepatitis B virus or other causes for CLDs, were excluded based on the laboratory data and liver biopsy. Pre-enrollment data included complete medical history, thorough clinical examination, abdominal ultrasound (CT if needed), ECG, fundus examination, and laboratory investigations including liver function tests, CBC, coagulation profile, Blood Chemistry, thyroid function, Viral markers, Auto-antibodies and liver biopsy. Finally, Serum Angiopoetin-2 (Ang-2) and Serum solubleTie-2 were determined by ELISA (Quantikine, R&D Systems, UK) before and after combination therapy. Then the patients were divided into 2 equal groups; 58 each according to type of peg-interferon given to each group. According to the national committee of viral hepatitis treatment, the patients received either Peg-interferon alfa 2a (pegferon 180µg) as a fixed dosage (manufactured by Memphis farm - Egypt) (Zeuzem et al., 2003)[9], or Peg-interferon alfa 2b (pegintron 100, 120 and 150 µg) by a dose of 1.5µg/kg body weight (manufactured by Schering Corp., a subsidiary of Merck & Co., Inc.), plus a Dose of ribavirin (600 -1200 mg), as a weight adjusted dosage, given orally each day in two divided doses with food [10] (manufactured by Sigma Pharm industries –Egypt /S.A.E. and Schering CO. /U.S.A.).All patients included in this study were submitted to follow up records at 12th weeks included: CBC with reticulocyte count- Liver enzymes (ALT/AST) - Bilirubin total and direct - Serum creatinine - HCV RNA PCR [for early viral response (EVR)]. Finally follow up records at 48th week included: Serum Angiopoetin-2 and serum-CBC with reticulocyte count- ALT and AST- Bilirubin total and direct - Serum creatinine - HCV RNA PCR [end of treatment response (ETR)].

Data analysis:-

Gathered data was processed using Statistical Package of Social Sciences version 10 (SPSS version 10 Inc., Chicago, IL, USA). Quantitative data was expressed as median or means ± standard deviation (SD) as appropriate. Qualitative data was expressed as frequency (numbers) and percentages. The results for all categorical variables were given in the form of rates (%). Student t test was used to test significance of difference for quantitative variables that follow normal distribution. Chi Squares and Fishers Exact tests were used to test significance of difference for qualitative variables. The independent data of the study was conducted and analyzed. Definitive statistics was used for the analysis of the socio-demographic and other variables. Firstly, the relation between the dependent and independent variables was studied using the Chi-square test and the t-test. Second, the significant variables were subjected to multivariate logistic regression analysis.

Results:-

In this study, (116) hepatitis C patients were involved, where all of them received interferon and ribavirin therapy at the center of viral hepatitis treatment at Ismailia fever hospital, Their age ranged between 23 and 57 years (mean= 42.5 ± 8.2), the majority (51.7%) were at age group from 40 to 50 year, and regardingtheir gender, 80 patients were males (69%) and 36 patients were females (31%).**Table (1)** shows the distribution of the patients according to response to treatment at week 12 {Early Virological Response (EVR)}, and week 48 {End of Treatment Response (ETR)}. Of the 116 patients included in the study, 99 patients (85.3%) had EVR where they completed the course to week 48 and 90 of them (90.9%) had ETR while 9 patients relapsed; so Sustained Virological Response (SVR) was obtained in 81 out of the 116 patients (69.8%). **Table (2)** shows the effect of combination therapy IFN/RBV on the serum level of Ang-2. There is a significant decline of serum Ang-2 after the end of treatment, week 48 (330.8 ± 73.0) compared to the baseline values (544.7 ± 64.1) in all patients whether had end of treatment response (ETR) or those who had no ETR (P<0.0 1).**Table (3)** shows the effect of combination therapy IFN/RBV on serum sTie-2(n=99). There is a significant increase of serum sTie-2after the end of treatment, week 48 (31.2 ± 1.04) compared to the baseline values (17.7 ± 2.1) in all patients whether had end of treatment response (ETR) or those who had no ETR (P<0.0 1).**Table (4)** shows a comparison between the mean pre-post changes (Δ) in Angiopoetin-2 & Tie-2between responders & non-responders at week 48. There is no difference between responders (212.5 ± 87.1) and non-responders (228.3 ± 22.9) at week 48 regarding serum Ang-2 and also there is no difference between responders (13.4 ± 2.4) and non-responders (14.22 ± 2.39) at week 48 regarding serum Tie-2(P<0.0 1).**Table (5)** shows the Correlation between Biopsy findings and baseline Angiopoetin-2 & Tie-2. There was a significant correlation between baseline sTie-2and grade of inflammation (0.242) (P<0.0 1). There was no correlation between baseline level of Ang-2 or sTie-2and stage of fibrosis, Spearman's Rank Correlation Coefficient (-0.020) and (-0.056) respectively (P<0.0 1). There was no correlation between baseline level of Ang-2 and grade of Inflammation, Spearman's Rank Correlation Coefficient (-0.061) and (-0.242) respectively (P<0.0 1).**Table (6)** shows the correlation between Lab. & clinical findings and baseline Angiopoetin-2 & its receptor TIE-2. There was a positive correlation between age and serum level of Tie-2 by 0.199 ($p<0.05$) that means that with increasing age there was an elevation of the serum level of Tie-2. Also, there was a negative correlation between white blood cell count and serum Ang-2 by 0.233 ($p<0.05$).

Discussion:-

Our prospective study was performed on the data collected from 116 patients with chronic HCV infection who were candidate for combination therapy in the center for treatment of viral hepatitis in Ismailia Fever Hospital, Egypt. The primary objectives of this study were to identify the effect of pegylated interferon and ribavirin therapy on the level of angiopoetin-2 and its receptor Tie-2 and to correlate the level of angiogenic factor angiopoetin-2 and its receptor Tie-2 with end of treatment response in chronic hepatitis C patients under combination therapy interferon/ ribavirin.We have to admit that Information on the pathophysiological role of the Ang/Tie-2 system in chronic inflammatory liver disease is rather scarce. Most of our knowledge gained by oncology studies, such as in hepatocellular carcinoma, in which the fundamental pathophysiological role played by angiogenesis has been well established [(11)], but generally speaking Ang-2 promotes a rapid increase in capillary diameter, remodeling of the basal lamina and vessel growth by facilitating sprouting [(12)], while the soluble form of the Tie-2 receptor functions as a natural inhibitor of Ang-2, and is therefore antiangiogenic [(13)].The mean age of our patients was 42.5 ± 8.2 years with a range of 23 – 57 years, where the frequency of male patients was higher than female patients (69% versus 31%, respectively); This comes in agreement with Several previous researches, which indicated a greater proportion of males are infected versus females[(14-16)]. In our study, there was a baseline elevated level of serum Angiopoetin-2 (Ang-2) in all patients (544.7 ± 64.1 in patients who achieved EVR, and 553.9 ± 24.9 in those who didn't achieve EVR at 12 weeks of therapy). Similarly, Salcedo et al. (2005)[(17)] found that the serum level of Ang-2 is a significantly higher in chronic hepatitis C (CHC) group compared to a control group, which indicated that Ang-2 may be more relevant to the pathophysiology of the disease; also in another study [(18)]it was reported that the mean levels of sAng-2 were significantly elevated in HCV, HBV and HCC patients when compared to that in the healthy control subjects. Regarding the response to the combination therapy with interferon and ribavirin in our study, there was a marked reduction in the serum marker Ang-2 before and after therapy at week 48 (545.1 ± 66.8 and 332.6 ± 75.7) respectively; more interestingly, the same reduction was observed also between patients who achieved ETR and those who didn't achieve it (540.7 ± 26.1 and 312.3 ± 33.8) respectively.Similarly, Salcedo et al. (2005)[(17)] founded that antiviral combination therapy markedly decreased Ang-2 levels in CHC patients. Also, Wada et al. (2007)[(19)] reported that interferon alpha treatment decreased the level of Ang-2 in hepatocellular carcinoma patients although it was combined with 5-fluorouracil and concluded that this combination has anti-proliferative and anti-

angiogenic effects, which we can say also for our combination therapy regardless the virological response; this can be powered by the fact that also, IFN-alpha has been successfully used in patients with pulmonary hemangiomatosis, [20] angioblastomas [21]and hemangioendotheliomas [22] which was via its anti-proliferative and anti-angiogenic effects by decreasing Ang-2 level. On the other hand, in our study, we found that combined therapy by IFN/RBV raised the level of serum sTie-2 from baseline levels to end of treatment levels (17.7 ± 2.1 and 31.2 ± 1.04) respectively; this finding is similar to that mentioned by Salcedo et al. [17] where he found a low level of the Ang-2 inhibitor sTie-2 receptor in 36 CHC patients were comparable to the 15 healthy controls which was markedly increased after combination therapy by IFN/RBV. However, in our study, serum Ang-2 and sTie-2 didn't express statistically significant change between responders and non-responders at 48 weeks, while Salcedo et al.[17] demonstrated a close relationship between variations in serum levels of angiogenesis markers and response to therapy in CHC patients; this may be due to the smaller number of their patients or differences in samples. As regards the relation between the angiogenic factors and viremia, we found that high level of viremia was associated with increased serum levels of Ang-2 and is inversely related to level of sTie-2 Vice versa; while in a study conducted by Helaly and Abou Shamaa [23] who studied the Influence of hepatitis C virus infection on circulating levels of VEGF (another angiogenic factor similar in action to Ang-2) in patients with hepatitis C and hepatocellular carcinoma (HCC), they found a weak correlation between the level of viremia and VEGF. In contrast to Salcedo et al. [17] who mentioned that determination of Ang-2 and sTie-2 in parallel to the viral load and fibrosis markers may provide complementary information to assess response to treatment and disease progression.Our results showed no statistically significant correlation between the grade of inflammation and stage of fibrosis and serum levels of Ang-2 and sTie-2; this also comes in agreement with the results of Salcedo et al.[17]However,Hernandez et al. [24] found that Ang-2 serum concentrations raised progressively with the stage of fibrosis. Although it was interesting to discover the effect of combination therapy by IFN/RBV on liver biopsy findings through its effect on Ang-2 and sTie-2, but for many ethical causes and of invasiveness of liver biopsy, we did not repeat the biopsy post-treatment. Finally, in our study, a significant correlation of Ang2 levels with prothrombin time was found and negative correlation for the albumin level; this comes in agreement with Kasztelan-Szczerbinska et al. [25] who mentioned that Ang-2 levels is related to synthetic liver function parameters, being positive for INR and negative for the albumin level, which suggested that Ang2 may be a relevant biomarker of liver function impairment and indicated the potential for its use in clinical practice. Moreover, in our study, we found a positive correlation of plasma Ang-2 concentrations with the liver enzyme ALT but no correlation with AST, which was Similar also to Kasztelan-Szczerbinska et al [25], who described a positive correlation of plasma Ang-2 concentrations with liver enzymes.

Table 1. Distribution of patients according to response to treatment at week 12 (EVR) and week 48 (ETR)

	Week 12 (EVR)		**Week 48 (ETR)**	
	No.	%	No.	%
Responders	99	85.3%	90	90.9%
Non-responders	17	14.7%	9	9.1%
Total	116	100.0%	99	100.0%

Table 2. the effect of combination therapy IFN/RBV on serum Ang-2 (n=99)

Markers	Response at 48-Week (ETR)	n	Mean ± SD (Range)		Mean ± SD	p-value
			Before Treatment "Baseline"	After Treatment "week 48"		
Angiopoetin-2	Responders (ETR)	90	545.1 ± 66.8 (460.0 – 927.0)	332.6 ± 75.7 (179.0 – 512.0)	212.5 ± 87.1	<0.001**
	Non-responders (no ETR)	9	540.7 ± 26.1 (487 - 568)	312.3 ± 33.8 (270 - 357)	228.3 ± 22.9	<0.001**
	Total	99	544.7 ± 64.1 (460.0 – 927.0)	330.8 ± 73.0 (179.0 – 512.0)	213.9 ± 83.4	<0.001**

**. Statistically significant difference at p<0.01; paired t-test

Table 3. the effect of combination therapy IFN/RBV on serum sTie-2(n=99)

Markers	Response at 48-Week(ETR)	n	Mean ± SD (Range)		Mean Difference ± SD	p-value
			Before Treatment "Baseline"	After Treatment "48-week"		
TIE-2	Responders (ETR)	90	17.8 ± 2.1 (15.0 – 24.1)	31.2 ± 1.01 (28.8 – 33.1)	13.4 ± 2.4	<0.001**
	Non-responders (no ETR)	9	16.9 ± 1.4 (15.5 – 19.4)	31.1 ± 1.39 (28.8 – 32.5)	14.22 ± 2.39	<0.001**
	Total	99	17.7 ± 2.1 (15.0 – 24.1)	31.2 ± 1.04 (28.8 – 33.1)	13.5 ± 2.41	<0.001**

**. Statistically significant difference at p<0.01; paired t-test

Table 4. Comparing the mean pre-post changes (Δ) in Angiopoetin-2 & TIE-2between responders & non-responders at week 48 (N=99)

Pre-Post changes (Mean ± SD)	Response To Treatment (at Week 48)		Mean Difference ± SE	p-value
	Responders (n= 90)	Non-responders (n= 9)		
Δ Angiopoetin-2	212.5 ± 87.1 (30.0 – 537.0)	228.3 ± 22.9 (192.0 – 256.0)	15.8 ± 29.3	0.590
Δ TIE-2	13.4 ± 2.4 (6.4 – 17.6)	14.22 ± 2.39 (10.1 – 16.8)	0.81 ± 0.84	0.340

**. Statistically significant difference at p<0.01; Independent samples t-test

Table 5. Correlation between Biopsy findings and baseline Angiopoetin-2 & its receptor TIE-2 (N =116)

	Spearman's Rank Correlation Coefficemt (p-value)	
	Angiopoetin-2	TIE-2
Stage of Fibrosis	-0.020 (0.828)	-0.056 (0.548)
Grade of Inflammation	-0.061 (0.513)	**-0.242(0.009**)**

**. Statistically significant difference at p<0.01

Table 6. Correlation between Lab. & clinical findings and baseline Ang-2 & TIE-2 (N = 116)

	Pearson's Correlation **Coefficient (p-value)**	
	Angiopoetin-2	**TIE-2**
Age (years)	0.083 (0.377)	**0.199 (0.032*)**
S. Albumin (g/dl)	0.108 (0.294)	0.028 (0.764)
S. Alkaline Phosphatase (IU)	0.074 (0.427)	-0.014 (0.882)
S. AST (IU)	-0.071 (0.447)	0.012 (0.894)
S. ALT (IU)	-0.035 (0.706)	0.029 (0.754)
T. Bilirubin (mg/d)	-0.007 (0.942)	-0.097 (0.298)
Indirect Bilirubin (mg/d)	-0.074 (0.427)	0.088 (0.348)
AFP	-0.056 (0.549)	-0.003 (0.977)
WBC × 10^3	**-0.233 (0.012*)**	-0.045 (0.631)
Hemoglobin (g/dl)	-0.005 (0.961)	-0.110 (0.241)
Prothrombin Time (sec.)	0.039 (0.675)	0.042 (0.654)
Blood Glucose (mg/d)	-0.167 (0.073)	0.004 (0.968)
S. creatinine (mg/d)	0.064 (0.494)	-0.033 (0.726)
TSH (IU)	0.035 (0.713)	-0.122 (0.191)
Interferon Dose	0.071 (0.448)	0.134 (0.150)
Ribavirin Dose	0.109 (0.244)	0.135 (0.148)
HCV-RNA PCR	0.004 (0.967)	-0.017 (0.859)

*. Statistically significant difference at p<0.05

Conclusion:-

Although Ang-2 and sTie-2 can't be used as a predictors of response to therapy, antiviral combination therapy markedly decreased serum Ang-2 levels and increased sTie-2 levels so it may be beneficial as a protective factor to reduce angiogenesis and consequently reducing hepatitis C related liver cirrhosis and HCC.

Ethical considerations:-

This study was approved by the University's Research Ethical Committee and an informed consent was taken from all the participants prior to recruitment into the study.

Conflicts of interest:-

We have not any conflict of interest to declare.

References:-

1- Lavanchy D. Evolving epidemiology of hepatitis C virus. Clin Microbiol Infect 2011; 17: 107–15.
2- El-Zanaty F and Way A. Egypt Demographic and Health Survey 2008. Egyptian:Ministry of Health (El-Zanaty and Associates and Macro International, Cairo), 2009; pp 431.
3- Fattovich G1, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors.Gastroenterology. 2004 Nov;127(5 Suppl 1):S35-50.
4- Esteban JI, Sauleda S, Quer J. The changing epidemiology of hepatitis C virus infection in Europe. J Hepatol. 2008; 48:148–162.
5- Stewart S, Day C. The management of alcoholic liver disease Hepatol 2003; 38 (Supp l. 1): S2–13.
6- S. Coulon, F. Heindryckx, A. Geerts, C. Van Steenkiste, I. Colle, H. Van Vlierberghe. Angiogenesis in chronic liver disease and its complications. Liver Int, 31 (2011), pp. 146–1627.
7- Yamamoto T, Hirohashi K, Kaneda K, et al. Relationship of the microvascular type to the tumor size, arterialization and dedifferentiation of humanhepatocellular carcinoma. Jpn J Cancer Res 2001; 92: 1207–13.

8- Yoshiji H, Kuriyama S, Fukui H. Blockade of reninangiotensin system in antifibrotic therapy. J Gastroenterol Hepatol 2007; 22(Suppl.1): S93–5.
9- Zeuzem S,Welsch C, Herrmann E. Pharmacokinetics of peginterferons. Semin Liver Dis 2003; 23(Suppl 1):23-28.
10- Mangia A, Minerva N, Bacca D, et al. Individualized treatment duration for hepatitis C genotype 1 patients: A randomized controlled trial. Hepatol. 2008; 47:43-50.
11- Semela D and J.-F. Dufour. "Angiogenesis and hepatocellular carcinoma," Journal of Hepatology. 2004; vol. 41, no. 5, pp. 864–880.
12- Visconti RP, Richardson C, Sato T. Orchestration of angiogenesis and arteriovenous contribution by angiopoietins and vascular endothelial growth factor (VEGF). Proc Natl Acad SciUSA. 2002; 99:8219-8224.
13- Carmeliet P. Angiogenesis in health and disease. Nat Med. 2003; 9:653-660.
14- Afdhal NH, Dieterich DT, Pockros PJ, et al. Epoetin alfa maintains ribavirin dose in HCV-infected patients: a prospective, double-blind, randomized controlled study.Gastroenterol. 2004; 126:1302-1311.
15- World Health Organization: Hepatitis C – global prevalence. Weekly Epidemiological Record, (2009); 75(3): 18–9.
16- Mohamed A. Abdel Mohsen, Neveen A. Hussein, Abeer A. Ghazal, et al. Angiogenic output in viral hepatitis, C and B, and HCV-associated hepatocellular carcinoma, Alexandria Journal of Medicine. 2014; vol 50, 235–240.
17- Salcedo X, Medina J, Sanz-Cameno P, et al. The potential of angiogenesis soluble markers in chronic hepatitis C. Hepatology. 2005; 42: 696-701.
18- Abdel-Mohsen M1, Deng X2, Danesh A2, Liegler T3, Jacobs ES2, Rauch A4, Ledergerber B5, Norris PJ6, Günthard HF5, Wong JK7, Pillai SK8. Role of microRNA modulation in the interferon-α/ribavirin suppression of HIV-1 in vivo.PLoS One. 2014 Oct 2;9(10.
19- Wada; Nagano; Yamamoto; et al. Combination therapy of interferon-α and 5-fluorouracil inhibits tumor angiogenesis in human hepatocellular carcinoma cells by regulating vascular endothelial growth factor and angiopoietins, Oncol Rep. 2007; Oct;18(4):801-9.
20- White CW, Sondheimer H, Crouch E, et al. Treatment of pulmonary hemangiomatosis with recombinant interferon alfa-2a. N Engl J Med.1989; 320:1197-1200.
21- Marler JJ, Rubin JB, Trede NS, Connors S, et al. Successful antiangiogenic therapy of giant cell angioblastoma with interferon alpha 2b: Report of 2 cases; pediatrics 2002, 109: E 37.
22- Palmieri G, Montella L, Martignetti A et al., Interferon alpha-2b at low doses as long-term antiangiogenic treatment of a metastatic intracranial hemangioendothelioma: a case report. Oncol Rep.2000; 7:145-149.
23- Helaly GF, Abou Shamaa LA. Influence of hepatitis C virus infection on circulating levels of sICAM-1 and VEGF in patients with hepatitis C and hepatocellular carcinoma (HCC) and their role in enhancing detection of HCC, Egypt J Immunol. 2006; 13(1):27-38.
24- Ángel Hernández-Bartolomé, Rosario López-Rodríguez, Yolanda Rodríguez-Muñoz, et al. Angiopoietin-2 Serum Levels Improve Noninvasive Fibrosis Staging in Chronic Hepatitis C: A Fibrogenic-Angiogenic Link, PLOS ONE | www.plosone.org 9 June 2013 | Volume 8 | Issue 6
25- Beata Kasztelan-Szczerbinska, 1 ,* Agata Surdacka, 2 Maria Slomka, 1 Jacek Rolinski, 2 Krzysztof Celinski, 1 Halina Cichoz-Lach, 1 Agnieszka Madro, 1 and Mariusz Szczerbinski 1. Angiogenesis-Related Biomarkers in Patients with Alcoholic Liver Disease: Their Association with Liver Disease Complications and Outcome. Mediators Inflamm. 2014; 2014: 673032. Published online 2014 May 18. doi: 10.1155/2014/673032.