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Role of Granulocyte Macrophage-Colony Stimulating Factor (GM-CSF) in Chronic Hepatitis B and C Infections

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GM-CSF is an important mediator of inflammation has been used to improve the immunological function of patients with various diseases and to ameliorate hematological disorders. We aimed at studying a possible role of GM-CSF in chronic viral hepatitis and to seek a rationale for its therapeutic use in such cases. Serum GM-CSF levels were found to be significantly elevated in all patient groups versus control. This elevation was significantly correlated with histological activity index (HAI) grade in the total group of patients with hepatitis, serum transaminases and with total leucocytic count (TLC), polymorphs, lymphocytes, monocytes and eosinophils. Stepwise regression analysis showed that HAI grades as well as polymorphs are the most potent significant predictive variables for serum GMC-CSF. Patients with leucopenia had significantly lower serum GM-CSF levels. GM-CSF may have a possible role in the pathogenesis of chronic viral hepatitis possibly by increasing the number of phagocytic cells. This might propose a rationale for the use of recombinant GM-CSF in patients with chronic viral hepatitis, especially those with leucopenia.

Key words: Granulocyte, macrophage, colony-stimulating factor, chronic hepatitis B, chronic hepatitis C, histological activity index, leucopenia

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Introduction

Colony stimulating factors are found in the serum, urine and certain tissues (Stanley *et al.*, 1975). Widely produced in the body, these regulators probably play an important role in resistance to infections. The granulocyte-macrophage colony-stimulating factors (GM-CSF) are well-characterized specific glycoproteins that interact to control the production, differentiation, and function of two related white cell populations of the blood, the granulocytes and monocyte-macrophages (Metcalf, 1985). They are produced in the body by several cell types including activated T and B lymphocytes, macrophages, eosinophils, endothelial cells, and fibroblasts (Metcalf and Nicola, 1995; Churchill *et al.*, 1992).
Recombinant human GM-CSF is commercially available and is used to improve the immunological function of patients with various diseases and to ameliorate hematological disorders (Martin *et al.*, 1993). However, its use in the treatment of chronic viral hepatitis is still controversial.

Materials and Methods

Patients: This study was conducted on forty patients selected from the Medical Outpatient Clinics in Mansoura University Hospitals. All of the cases had histopathological evidence of chronic hepatitis and were divided into 3 groups:

Group I: Twenty-six patients with chronic hepatitis C infection. All were positive for the presence of hepatitis C (by second generation ELISA and polymerase chain reaction). They were 14 females (53.8%) and 12 males (46.2%). Their mean age ± standard deviation was 40.3 years ± 9.7.
Group II: Eight patients with chronic hepatitis B infection. All were positive for HbsAg. They were 6 males' (75%) and 2 females (25%). Their mean age ± standard deviation was 37.6 years ± 13.6.
Group III: Six patients with mixed hepatitis B and C infections. All were positive for both HbsAg and Anti-HCV antibodies. They were 3 females' (50%) and 3 males (50%). Their mean age ± standard deviation was 42.7 years ± 11.8.

Exclusion Criteria: Cases with advanced liver disease, cases associated with another inflammatory condition including associated HIV infection, cases with schistosomiasis, cases complicated by hepatocellular carcinoma, and cases receiving anti-viral therapy were excluded.

Control group: The study also involved 10 healthy individuals as a control group for serum GM-CSF levels. They were 6 females (60%) and 4 males (40%). The mean age ± standard deviation was 39.6 years ± 10.54.

All cases were subjected to the following:

1. Thorough history taking with special stress on symptoms of chronic liver disease, musculoskeletal symptoms, and possible risk for exposure to infection.
2. Thorough physical examination with special stress on general signs of chronic liver disease and liver cell failure and local abdominal examination.
3. Laboratory investigations were done including complete blood count, urine and stool analysis, and serum creatinine.
4. Sigmoidoscopy with rectal snip searching for bilharzial ova.
5. IHA test for Schistosomiasis.
6. Biochemical liver function tests including liver enzymes, prothrombin time, serum albumin, and serum bilirubin.
7. Serum GM-CSF levels (by using the Titer Zyme GM-CSF Enzyme Immunoassay Kit).
8. Abdominal ultrasound with special stress on liver (for masses), splenic enlargement, and ascites.
9. Percutaneous tru-cut liver biopsies:
   For histopathological diagnosis of chronic hepatitis. For assessment of disease severity and progression utilizing the grading and staging system of Ishak *et al*. (1995)

Grading (An estimate of severity)	
A. Periportal or periseptal interface hepatitis (= Piecemeal necrosis)	0 - 4
B. Confluent necrosis	0 - 6
C. Focal (Spotty) lytic necrosis, apoptosis and focal inflammation	0 - 4
D. Portal inflammation	0 - 4
TOTAL SCORE	0 - 18
Staging (An estimate of progression)	
Architectural changes, fibrosis and cirrhosis	0 - 6

Statistical analysis: Values were expressed as counts and percentages (compared by the Chi-Square test), or mean ± SD (compared by the Independent-Samples T-test). Kruskal-Wallis test was used to compare sets of data in three or more groups when the data were non-parametric or did not follow the normal distribution. Linear correlation between two variables was performed by the Pearson or Spearman's rank (for non-parametric data) correlation tests. Multiple linear regression analysis was used to predict the effect of a group of variables on a dependent one. Stepwise multiple regression analysis was used to determine the most potent effective predictors among a group of different independent variables. All statistical calculations were performed using a computer program (SPSS for windows, SPSS Inc., 1989 - 1996).

Results

The clinical, biochemical and hematological data: The results of some important aspects of the history and clinical examination are displayed in Table 1. Fatigue as well as musculoskeletal pain are noticed to be significantly higher in HCV versus HBV patients (*Chi-Square* = 5.988 and 5.535, p = 0.014 and 0.019, respectively).
The biochemical and hematological data of the three groups of patients as well as the control group are shown in Tables 2 and 3, respectively. The serum transaminases and bilirubin are significantly higher in each of the three examined patient groups as compared to the control patients. However, only a fraction of patients had abnormally high values of the parameters mentioned. Both bilirubin and the transaminases have been statistically indifferent between the three groups.
The mean values of the total leucocytic count (TLC) as well as the polymorphonuclear leukocyte count have been significantly lower in the hepatitis patients, whether due to virus C, B, or mixed infection, when compared to the control group. On the other hand, the mean lymphocytic counts of group I and group II, but not group III patients, have been significantly lower than that of the control group (Table 3). Leucopenia (defined as TLC of less than 4000/cmm) has been found in 11.5 % (3/26) of group I cases, in one quarter (2/8) of group II cases, and in 16.67% (1/6) of group III cases.

The Histological Activity Index: The frequency distribution of individual histological grades (scores) and stages (according to Ishak *et al.*, 1995) among the three groups of patients is shown in Table 4. There has been no significant difference in distribution of HAI grades or stages among the three studied groups of patients.
Similarly, although group I patients have had relatively higher values for HAI grades, statistical analysis of the sets of data

of grades and stages among the three groups of patients has revealed non significant differences (Table 5). In the total patient group, the HAI scores have shown significant correlation with serum transaminases, total leucocytic count, polymorphonuclear cell count and lymphocytic count Table 6.

Serum GM-CSF in the Studied Groups: Serum GM-CSF level has been found to be higher than normal in 100% of the hepatitis patients. In all the studied patient groups, the mean as well as the median serum GM-CSF has shown a marked increase (16-22-folds) in comparison to the control group. The mean as well as the median serum level has also been significantly higher in both group I and group III patients than that in group II patients; the difference between groups I and III is not statistically significant Fig. 1 and Table 7.

Linear correlation tests between serum GM-CSF level and different biochemical, hematological and histopathological parameters in the total patient group have shown significant linear association between GM-CSF and serum transaminases, TLC and most of its constituents, and HAI grade (Table 8). On analyzing each group of patients separately, Spearman's rank correlation has revealed strong association between serum GM-CSF and the HAI grade (for group I $r_s = 0.878$, $p < 0.001$; for group II $r_s = 0.994$, $p < 0.001$; and for group III $r_s = 0.883$, $p = 0.020$). Similarly, Pearson's linear correlation has revealed strong relation between serum GM-CSF and both AST and ALT in each group of patients (for group I $r = 0.705$ and 0.695. $p < 0.001$; for group II $r = 0.948$ and 0.948, $p < 0.001$; and for group III $r = 0.863$ and 0.881, $p = 0.027$ and 0.020, respectively). Multiple linear regression analysis of the studied biochemical, hematological and histopathological parameters, as independent variables, on the serum GM-CSF, as the dependent variable, has revealed significant predictive value of both HAI grade (score), serum transaminases, and polymorphonuclear cell count (Table 9). Stepwise regression analysis has excluded all parameters but the HAI grade and, to a lesser extent, the polymorphonuclear count as the most important significant predictive variables of changes of serum GM-CSF Table 10.

Among the studied patients of hepatitis, 6 cases have had leucopenia with TLC below 4000/cmm. Comparing the mean as well as the median level of serum GM-CSF in the leucopenic Vs non-leucopenic patients has revealed significantly lower level in the cases with leucopenia Fig. 2 and Table 11.

Discussion

Chronic hepatitis is a "smoldering" inflammation of the liver that lasts six months or longer (Carl, 1998). Clinically, symptoms range from none to incapacitating exhaustion (Sherlock, 1993). The most important general symptom is fatigue. Physical signs include jaundice, vascular spiders (rarely), a large or small liver, and splenomegaly (Sherlock, 1994). Barkhuizen *et al*., 1999, found that musculoskeletal pain and fatigue are more frequent among patients with isolated hepatitis C infection than among patients with isolated hepatitis B. Musculoskeletal pain was found in 88.46% of group I, in 83.33% of group III, and in only one half of group II cases. Similarly, fatigue was found in 73.1 % of group I, in 66.67% of group III, and in only one quarter of group II cases. So, musculoskeletal complaints are more frequent among patients with hepatitis C whether 'isolated' or 'mixed' with hepatitis B infection than among patients with 'isolated' hepatitis B infection.

Chronic hepatitis B has long been known to be related to the ethnic origin of the patient, homosexuality, drug abuse, or a likely contact with blood of patients carrying hepatitis B. Chronic hepatitis C is usually acquired from infected blood or blood products or by parenteral drug use, the mode of infection is unknown in many instances (Sherlock, 1994). In our study, patients of the three groups gave history of exposure to many of the possible risk factors including blood transfusion (7.69, 25, and 33% for groups I, II and III, respectively), dental & surgical procedures (69.23 and 11.54% for group I, 80 and 12.5% for group II, and 50 and 16.67% for group III, respectively), and parenteral drug use (100% for all groups).

Abnormal biochemical test results suggestive of chronic hepatitis include a modestly elevated serum bilirubin level and increased levels of aminotransferases (Sherlock, 1994). In our study, serum bilirubin level was modestly but significantly elevated in all patient groups (I, II, and III) versus control ($p = 0.009$, 0.001 and 0.015, respectively). Clinically, jaundice was elicited in only 11.5% of group I, in only one case from group II (12.5%), and in one third of group III (33%). Similarly, AST and ALT were significantly elevated in all patient groups versus control.

Low white cell count has long been known to associate some chronic viral hepatitis cases, especially if the spleen is enlarged (Sherlock, 1994). Significantly lower values for TLC, polymorphs and lymphocytes in both groups I & II versus control group ($p = 0.002$, 0.013, and 0.001 for group I, and 0.010, 0.003, and 0.077 for group II, respectively). Leucopenia (defined as TLC of less than 4000 cells / cmm) was found in 11.5% of group I cases, in one quarter of group II cases, and in 16.67% of group III cases.

The terms chronic active hepatitis, chronic persistent hepatitis and chronic lobular hepatitis have become obsolete, and one should not use them without further specifications (Batts and Ludwig, 1995). Therefore, many systems have been developed for scoring liver histology in chronic hepatitis. They vary from simple ones (Lok *et al*., 1985; Scheuer, 1991; Ludwig, 1993), with a relatively restricted range of numbers, to more complex and detailed schemes (Knodell *et al*., 1981 and Bedossa *et al*., 1994). The most widely used is the Histological Activity Index (HAI), also known as the Knodell score (Knodell *et al*., 1981). In order to confirm the diagnosis of chronic hepatitis and relate changes of the histopathological severity to the other studied parameters, we performed percutaneous liver biopsies for all patients and examined them according to the grading and staging system of Ishak *et al*., 1995.

We found no significant difference in the histopathological grade (an estimate of severity) or stage (an estimate of progression) among the three groups of patients. The HAI grade showed significant positive linear correlation with serum transaminases and leucocytic count. This may provide assuring support to the validity of the HAI grade as a reflection of the disease activity of hepatitis. The absence of significant difference in HAI grade between the different groups of patients, together with the absence of significant differences in serum transaminases among them, may indicate comparable severity of the hepatitis in the three groups of patients.

Chronic active hepatitis is the liver disease *par excellence* where immunological factors are invoked in the perpetuation of liver cell injury (Sherlock, 1993). Liver histology shows heavy infiltration by lymphocytes and plasma cells with periportal piecemeal necrosis suggesting a type IV hypersensitivity reaction (Sherlock, 1993). Immune-mediated mechanisms are believed to play an important pathogenetic role in chronic hepatitis C (Reiser *et al*., 1997). Quiroga *et al*., 1994 found that HCV patients have an altered immune reactivity that might play a role in the pathogenesis of chronic hepatitis C. Also, it is thought that lymphocyte function is broadly deranged in chronic hepatitis B (Alexander and Eddleston, 1986). Interleukin 1 production by monocytes from patients with chronic hepatitis B is increased (Anastassakos *et al*., 1988).

The growth and differentiation of colonies of granulocytes and/or monocytes-macrophages require the presence of "colony stimulating" factors; granulocyte-colony stimulating

factor (G-CSF) and granulocyte macrophage colony stimulating factor [GM-CSF] (Stanley *et al.*, 1975). These factors are not simply proliferative stimuli but they can also regulate the functional activity of mature cells (Metcalf, 1986). They are found in serum, urine and certain tissues (Stanley *et al.*, 1975). Widely produced in the body, these regulators probably play an important role in resistance to infections (Metcalf, 1985). While G-CSF stimulates the production of neutrophils and stem cell division; GM-CSF neutrophil, monocyte, eosinophil, erythroid and megakaryocytic cell growth (Lieschke and Burgess, 1992 and Metcalf and Nicola, 1995). A significant elevation (16-22-fold) of serum GM-CSF in all patient groups versus the control group. In accordance with our results, Kountouras *et al.*, 1998 reported increased GM-CSF level in chronic hepatitis B infection and suggested that it might serve to monitor viral activity and outcome of patients. However, the results showed that serum GM-CSF is statistically significantly higher in HCV compared to HBV patients. A significant positive correlation between serum GM-CSF levels, on one side, and the histological marker of severity (HAI grade) and liver enzymes, on the other side; both in the total group of patients as well as in the HCV, HBV and mixed infection subgroups of patients, considered separately. Therefore, it may not be difficult to conceive that serum GM-CSF levels can be used to monitor activity of chronic hepatitis, not only in HBV but also in HCV infections.

In our study, there was a significant positive correlation, in the 'total' patient group, between serum GM-CSF level, on one side, and TLC, polymorphs, lymphocytes, eosinophils and monocytes, on the other side. Based on the fact that GM-CSF stimulates the proliferation and maturation of myeloid progenitor cells giving rise to polymorphs and monocytes thus increasing the number of phagocytic cells, one would be logic to think about a possible role of such cytokine in the host defense against chronic viral hepatitis.

Thus, it is tempting to postulate that giving GM-CSF exogenously to chronic hepatitis patients might help in clearing the viral infection. Actually, recombinant human GM-CSF is being used to improve the immunological function of patients with various diseases and to ameliorate hematological

Table 1: Clinical profile in the three patient groups

Characteristic	%(Group I)(n=26)	%(GroupII)(n=8)	%(Group III)(n=6)
1- Possible risk factors for exposure to infection			
a. Hepatitis among cohabiting	11.54	25.0	16.67
b. Parenteral drug use	100.0	100.0	100.0
c. Previous hospital treatment	34.6	37.5	33.0
d. Dental procedures	69.23	80.0	50.0
e. Surgical procedures	11.54	12.5	16.67
f. Blood transfusion	7.69	25.0	33.0
2- Fatigue	73.1	25.0	66.67
3- Musculo-skeletal pain	88.46	50.0	83.33
4- Jaundice	11.54	12.5	33.0
5- Spider nevi	7.69	25.0	33.0
6- Liver flap	3.85	0.0	0.0
7- Sharp-edged firm liver	11.54	12.5	16.67
8- Splenomegaly	11.54	12.5	16.67
9- Ascites	0.0	0.0	16.67

Table 2: Biochemical data in the three patient groups Vs control

		Control	Group I	Group II	Group III
Serum bilirubin (mg/dl)	Mean±SD	0.84±0.126	1.25±0.456	1.26±0.28	1.28±0.49
	Vs control	t	2.778	4.25	2.96
		p	0.009	0.001	0.015
	% of high values		46.15%	50.0%	33.0%
AST (IU/L)	Mean±SD	29.4±6.7	67.19±30.3	58.1±27.7	55.0±25.1
	Vs control	t	3.875	3.18	3.11
		p	<0.001	0.006	0.008
	% of high values		69.23%	62.5%	50.0%
ALT (IU/L)	Mean±SD	26.4±5.7	68.15±28.5	63.1±27.7	57.5±28.1
	Vs control	t	4.56	4.11	3.47
		p	<0.001	0.001	<0.001
	% of high values		76.92%	62.5%	50.0%

Table 3: Hematological data in the three patient groups Vs control

		Control	group I	Group II	Group III
TLC (per cmm)	Mean±SD	6262 ±921	5092.0±954	4750.0 ±1269	5867.0 ±1587
	Vs control	t	-3.326	-2.932	-0.638
		p	0.002	0.010	0.534
Polymorphs (per cmm)	Mean±SD	3705 ±580	3154. ±0555	2700.0 ±659	3183.0±749
	Vs control	t	-2.635	-3.439	-1.565
		p	0.013	0.003	0.140
Lymphocytes (per cmm)	Mean±SD	2312±470	1688.0±453	1771.0±743	2300.0±892
	Vs control	t	-3.665	1.888	-0.037
		p	0.001	0.077	0.971
Eosinophils (per cmm)	Mean±SD	103±23	113.0±25	98.0±11	93.0±10
	Vs control	t	1.038	-0.611	-1.101
		p	0.307	0.550	0.289
Monocytes (per cmm)	Mean±SD	104±22	105.0±20	98.0±13	93.0±14
	Vs control	t	0.079	-0.743	-1.069
		p	0.937	0.468	0.303
Basophils (per cmm)	Mean±SD	33±6	32.0±9	34.0±8	31.0±7
	Vs control	t	-0.060	0.362	-0.500
		p	0.953	0.722	0.625

Table 4: Frequencies of HAI grades and stages in the three patient groups

	Group I count (%)	Group II count (%)	Group III count (%)
Grade			
3	1 (3.8)	1 (12.5)	0 (0)
4	2 (7.7)	1 (12.5)	0 (0)
5	1 (3.8)	2 (25)	0 (0)
6	2 (7.7)	1 (12.5)	1 (16.67)
7	2 (7.7)	1 (12.5)	0 (0)
8	2 (7.7)	0 (0)	0 (0)
9	2 (7.7)	0 (0)	2 (33.3)
10	6 (23.1)	1 (12.5)	1 (16.67)
11	4 (15.3)	0 (0)	2 (33.3)
12	3 (11.5)	1 (12.5)	0 (0)
14	1 (3.8)	0 (0)	0 (0)
Fisher's exact test value = 15.55, (p = 0.792)			
Stage			
1	3 (11.5)	1 (12.5)	1 (16.67)
2	6 (23.1)	2 (25)	2 (33.3)
3	7 (27.0)	2 (25)	0 (0)
4	3 (11.5)	1 (12.5)	1 (16.67)
5	4 (15.3)	1 (12.5)	1 (16.67)
6	3 (11.5)	1 (12.5)	1 (16.67)
Fisher's exact test value = 3.985, (p = 0.995)			

Table 5: Statistical analysis of HAI grades and stages among the three patient groups

		Group I	Group II	Group III	Kruskal-Wallis test
Grades	Mean	8.85	6.50	9.33	p = 0.147
	SD	2.85	3.07	1.86	
	Median	10.00	5.50	9.50	
Stages	Mean	3.30	3.25	3.33	p = 0.993
	SD	1.57	1.67	1.97	
	Median	3.00	3.00	3.00	

Table 6: Rank correlation (Spearman) and significance of HAI and some biochemical and hematological parameters

		Serum bilirubin	AST	ALT	TLC	PMNs	Lympho- cytes
HAI grade	r_s	0.124	0.644	0.610	0.701	0.699	0.675
	p	0.445	<0.001	<0.001	<0.001	<0.001	<0.001
HAI stage	r_s	-0.133	0.062	0.090	0.240	0.332	0.099
	p	0.412	0.705	0.579	0.136	0.036	0.543

Table 7: serum levels of GM-CSF (pg/ml) in all studied groups

	control	Group I	Group II	Group III
Mean	2.87	63.23	46.00	64.83
SD	0.275	10.80	10.80	6.37
Vs control	t	17.56	12.727	31.471
	p	<0.001	<0.001	<0.001
Vs group I	t	3.955	-0.348	
	p	<0.001	0.730	
Vs group II	t	-3.785		
	p	0.003		

Table 8: Correlation between serum GM-CSF levels and biochemical and hematological data and histological findings among total group of patients

Parameter	Total group of patients (n = 40)	
	Coefficient	p
Serum bilirubin[a]	r = 0.199	0.218
AST[a]	r = 0.654	<0.001
ALT[a]	r = 0.626	<0.001
TLC[a]	r = 0.738	<0.001
Polymorphs[a]	r = 0.776	<0.001
Lymphocytes[a]	r = 0.589	<0.001
Eosinophils[a]	r = 0.448	0.004
Monovytes[a]	r = 0.464	0.003
Basophils[a]	r = 0.049	0.764
HAI grade[b]	r_s = 0.925	<0.001
HAI stage[b]	r_s = 0.165	0.310

[a] Pearson's correlation test
[b] Spearman's rank correlation

disorders (Martin *et al.*, 1993).

Van Thiel *et al.*, 1997 found that the combination of GM-CSF and interferon (IFN) might be more effective at achieving viral clearance than IFN alone in patients with chronic viral hepatitis especially those who are considered untreatable because of advanced disease and leucopenia. Also, Carreno *et al.* (1996) found that GM-CSF might potentiate the virologic response to IFN-alpha treatment. In contrast, Shiffman *et al.* (1998) found that GM-CSF either alone or in combination with interferon does not appear to be effective for treatment of chronic HCV.

Based on the finding of frequent leucopenia in chronic viral hepatitis patients and that serum GM-CSF is lower in the subset of patients with leucopenia, we may propose that GM-CSF can be a useful therapeutic agent in patients with chronic

Table 9: Coefficients and significance of multiple regression analysis of different biochemical, hematological and histopathological predictor variables on serum GM-CSF

	B	Std. Error	Beta	t	p
Bilirubin	0.997	2.812	0.034	0.355	0.726
AST	0.572	0.209	1.344	2.741	0.011
ALT	-0.586	0.212	-1.325	-2.759	0.010
TLC	-0.011	0.006	-1.005	-1.756	0.090
Polymorphs	0.016	0.007	0.790	2.127	0.043
Lymphocytes		0.011	0.006	0.535	1.896
0.069					
Eosinophils	0.009	0.052	0.016	0.165	0.870
Monocytes	0.041	0.061	0.062	0.675	0.505
Basophils	-0.021	0.098	-0.015	-0.213	0.833
HAI grade	3.000	0.424	0.705	7.073	<0.001
HAI stage	-0.507	0.476	-0.066	-1.065	0.296

Table 10: Coefficients and significance of stepwise regression analysis of different biochemical, hematological, and histopathological independent

Model	Variable	B	Std. Error	Beta	t	p
1	HAI grade	3.935	0.262	0.925	15.007	<0.001
2	HAI grade	3.280	0.326	0.771	9.050	<0.001
	PMNs	0.004	0.002	0.210	2.464	0.019

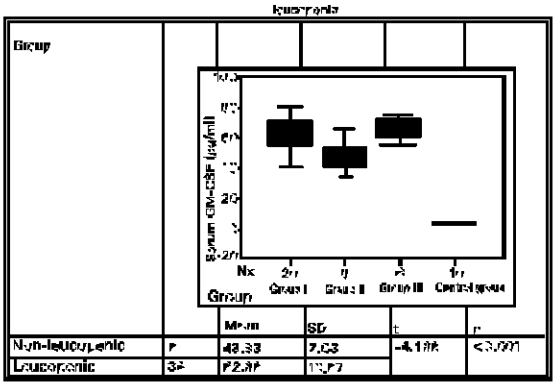

Fig. 1: Boxplot for serum GM-CSF in the three patient groups Vs control

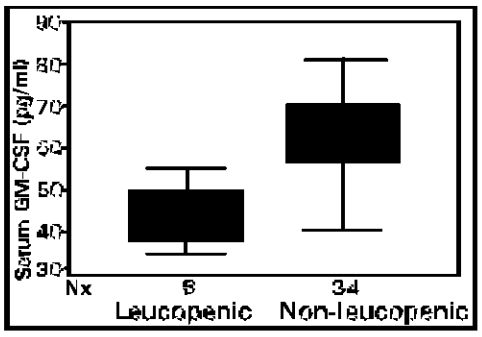

Fig. 2: Boxplot for serum GM-CSF in the leucopenic Vs non-leucopenic group

hepatitis B and / or C infection especially those who are leucopenic. GM-CSF may stimulate the hematopoietic regeneration and the functional activity of granulocytes and monocytes, thus improving the immune status of patients, which is implicated in the pathogenesis of the disease. However, it is difficult to anticipate who will get more benefit from GM-CSF therapy: those who initially present with leucopenia, or readily develop it after institution of interferon therapy, and fail to mount an appropriate GM-CSF response, or those who already present with an excessive serum GM-CSF response.In conclusion, GM-CSF is increased in the serum of patients with chronic viral hepatitis where its level might be predicted by the histological and clinical severity of the disease as well as the polymorphonuclear cell count. It is suggested that it may be involved in the pathogenesis of such condition and can be useful in monitoring disease activity. It may be proposed that GM-CSF could be beneficial in treating at least a sector of chronic hepatitis patients, especially those who have leucopenia.

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