Estimation of cellular immune response by evaluation of some cytokines in immunopathogenesis of chronic hepatitis B and C pre- and post- treated Iraqi patients (in vivo and in vitro)

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Nawal Mahdi Al-khalidi**

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Abstract:
Two groups of chronic hepatitis B and C virus patients were divided into Pre-treated patients (25 CHB patients with positive HBs Ag for more than 6 months and 40 CHC patients), and post-treated patients [12 CHB patients (4, 6, and 2 were treated with lamivudine, IFN-α and combination of LMV + IFN-α respectively), and 27 patients for CHC (3, 13 and 11 patients were treated with Ribavirin, IFN-α and combination therapy (RBV+ IFN-α) respectively]. These patients were followed up for 6 months.

By using ELISA technique, levels of IL-6, IL-10, IFN-γ and TNF-α were measured in vivo and in vitro (supernatant of PBMCs stimulated with PHA) and compared with healthy control. The mean level of IL-6, IL-10 and TNF-α in CHB patients showed significant differences (P<0.05) between pre- and post-treated patients in vivo and in vitro, while there was no significant difference in IFN-γ between pre- and post-treated patients in vivo and in vitro. The difference between control and CHB patients was highly significant (P<0.0001) in IL-6, IL-10 and TNF-α levels in vivo and in vitro. In CHC patients the mean levels of IL-6, IL-10, IFN-γ and TNF-α showed significant difference between pre- and post-treated patients in vivo and in vitro. There was highly significant difference (P<0.0001) between patients and control in IL-10 levels. Hence, these observations indicate the predominance of Th2 cytokine, which promote the persistency of the CHB and CHC virus.

Key words: cellular immune response, cytokines, chronic hepatitisB, chronic hepatitisC, IFN-γ, TNF-α

Introduction:
Cytokines are small molecules that act as a means of communication between cells, thus have many roles within the liver. Cytokines play an important role in the defense against viral infections, both indirectly, through determination of the predominant pattern of host response, and/or directly, through inhibition of viral replication. However, within the context of an inflammatory response against a virus, Cytokines may also lead to liver damage [1].

It was reported that HBV infection is associated with the production of a broad range of proinflammatory cytokines and chemokines such as IL – 1 β, IL – 6, IL – 8, IL – 12 and IFN - γ. As well as the anti-inflammatory cytokine IL – 10 [1,2,3]. In HCV, the cytokines present at the initiation of immune response are the most clearly defined factors determining Th1 and Th2 differentiation from Th0 [4]. Proinflammatory cytokines such as IFN – γ and TNF – α are increased and they
attributed to an imbalance in Th1, and Th2 CD4+ cell activity with a predominant T helper 1 cell response [5]. Tumor necrosis factor – α (TNF – α), interleukin – 6 (IL – 6) are important mediators of the inflammatory response. Monocytes are considered to be the main – producers of these monokines, but along list of potential cell sources have been reported. Some of these reports indicate that peripheral T cells can produce TNF – α, IL – 6 and IL – 1 [6,7] demonstrated that monokines release was totally inhibited by anti - IFN – γ treatment indicating that TNF-α and IL – 6 were both induced by IFN – γ. Production of IL – 6 and TNF – α is certainly stimulated Th1 derived lymphokines, and IFN – γ act as macrophage – activating factor and to induce monokines release [6].

Proteins whose expression was reported to be elevated in chronic HCV infection are IFN – γ [8], and class I and class II major histocompatibility complex (MHC) [9], which are known to be regulated by IFN – γ, as well as the accessory molecules CD80, CD86, and B7. In addition to CD8+ lymphocytes and monocytes, preferentially antigen – non specific activated Th1 lymphocytes are attracted to the liver. By secreting IFN – γ, the latter cells are thought to activate monocytes, macrophages, thereby initiated a delayed type hypersensitivity reaction [8].

The cytokines may down regulate HCV specific cellular immunity and promote viral persistence [10]. Higher serum IL – 10 levels correlate with a poor response to treatment, a sustained treatment response has been associated with decreased IL – 4 and IL – 10 [11].

So that the purpose of this study was: Evaluation of possible role of Th1 cytokine IFN-γ and Th2 cytokines: IL-6, IL-10, and other inflammatory cytokines such as TNF-α, in immunopathogenesis of chronic hepatitis B and C pre- and post- treated patients (in vivo and in vitro) (supernatant of PBMCs stimulated with PHA).

**Materials and Methods:**

**Subjects**

Across sectional study was conducted on the following study groups for the period from September 2004 to October 2005:

A total of sixty five (65) patients of both sexes were divided into two major groups:

* Twenty-five (25) patients with chronic hepatitis B- virus (CHBV) (marked with appearance of hepatitis B surface antigen HBs-Ag and persisted more than 6 months). This marker in the sera was detected by using Enzyme-Linked Immunosorbent Assay (ELIZA), these patients consisted of 18 males and 7 females, with age ranged between (25-73) years.

* Forty (40) patients with chronic hepatitis C- virus (CHCV) (marked with appearance of anti- hepatitis C antibodies in their sera and persist more than 6- months which was detected by using ELIZA- technique). These patients included 21-males and 19- females and were of age ranged between (6-60) years.

All these patients showed increasing levels in liver function tests (TSB, SGPT, SGOT, and SALP) and they had been clinically diagnosed according to the previous laboratory test and the clinical examination when they were inpatients admitted in Gastroenterology and Hepatology Teaching Hospital.

**Normal control group:** Fifteen (15) healthy persons of different age and sex were randomly selected as normal control (NC) during the period of this study.
Collection of Blood Samples
Ten ml of venous blood was drawn from each subject aseptically.
* Serum from 4 ml of blood sample was used for the evaluation of interleukins.
* A volume of 3.75 ml of blood sample was collected in sterile evacuated tubes containing heparin for lymphocytes transformation assay using "3ml blood for purified lymphocytes " and "0.75ml blood for Whole blood ".

Lymphocyte transformation assay by using Separated lymphocytes.
A. Lymphocyte separation
Peripheral blood mononuclear cells (PBMCs) were isolated by Ficoll-Hypaque density gradient method, principally as described by Boyum [12].
B. Viability test: The viability was determined by trypan blue dye exclusion test [13].
C. Preparation of culture: This assay was done according to Kanto et al[4].
* A volume of 2.75 ml of separated lymphocytes (1 x 10^6 cell/ml RPMI 1640) was cultured in sterile silicon coated tubes.
* A volume of 250μl of mitogen (PHA) was added to one of these tubes (test), while the other tube left without any addition of mitogen (control).
  • The ratio of transformed cells was calculated by the following equation:

\[
\text{Transformed cells } \% = \frac{\text{No. of transformed cells}}{\text{Total No. of cells count}} \times 100
\]

Determination of Cytokines
Cytokines levels in both serum and supernatant of separated lymphocytes culture were determined. The cytokines that used in this assay were IFN-γ, IL-6, IL-10 and TNF-α, and they were measured by means of enzyme linked immunosorbent assay, using ELISA kits (Mabtech AB, Sweden) as recommended by the manufacture.

Statistical analysis
Student’s t test of significance was used for two- groups’ comparison when the data were quantitative in nature. The Chi- square (X^2 ) test for significance was adopted for the comparison and calculation of association in qualitative data. The statistical significance of difference in mean of variable between more than two groups was assessed by ANOVA test [14]. Probability values of P<0.05 were considered statistically significant.

Results and Discussions:
Estimation of cytokine levels in vivo and in vitro pre- and post- treatment
To know whether an imbalance between Th1 and Th2 cytokines are present in patients with CHB and CHC infection, with and without treatment in vivo and in vitro(PBMCs supernatant harvested after 3 days of incubation stimulated by PHA) in comparison to that of healthy control group, levels of Th1 cytokines (IFN-γ) and Th2 cytokines (IL-6, IL-10) and inflammatory cytokine (TNF-α) were measured using enzyme-linked immunosorbent assay in this study.

1 Level of IL-6
The result of this study revealed high mean values of IL-6 levels pg/ml in CHB patients pre-treatment that are shown in table (1), as compared to healthy controls both in vivo (P= 0.000) and in vitro (P= 0.000) (PBMCs supernatant stimulated with PHA). Also the present study showed that there was highly significant difference in IL-6 levels between pre- and post-treated CHB patients in vivo and in vitro (stimulated with PHA and non stimulated) (P < 0.05), this results was coincided with the results of Lee et al [15] who reported that IL-6 can be induced by HBV-X protein as evidenced by high levels of serum IL-6.
in patients with CLD with HBV infection. Preliminary experiments determined that lymphokine levels in the culture supernatants of both normal subjects and chronically infected HBV patients peaked after 3 days [16]. They showed that the patients who failed to mount a proliferative response also failed to secrete any of the cytokines under study.

Table (1): - Comparison in cytokine levels between (25) pre- and (12) post-treated CHB patient in vivo and in vitro.

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Source</th>
<th>Pre-treatment* (25)</th>
<th>Post-treatment* (4)</th>
<th>IFN-α2b (6)</th>
<th>IFN-α2b (12)</th>
<th>P Value</th>
<th>Control (15)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6</td>
<td>Serum</td>
<td>4.92±52.40</td>
<td>55.5±18.17</td>
<td>7.8.0±426.16</td>
<td>46.0±8.48</td>
<td>0.008</td>
<td>38.8±27.65</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>supernatant stimulated with PHA</td>
<td>89.2±65.60</td>
<td>87.5±6.57</td>
<td>125.0±76.70</td>
<td>95.0±4.24</td>
<td>0.011</td>
<td>42.6±10.60</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>supernatant without stimulation</td>
<td>8.81±5.60</td>
<td>0.45±0.23</td>
<td>0.55±0.35</td>
<td>0.45±0.01</td>
<td>0.07</td>
<td>0.33±0.11</td>
<td>0.49</td>
</tr>
<tr>
<td>IL-10</td>
<td>Serum</td>
<td>48.0±42.34</td>
<td>76.75±48.94</td>
<td>51.5±24.44</td>
<td>46.25±3.50</td>
<td>0.011</td>
<td>18.5±16.02</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>supernatant stimulated with PHA</td>
<td>58.5±44.05</td>
<td>63.25±50.88</td>
<td>36.50±6.94</td>
<td>30.1±6.00</td>
<td>0.002</td>
<td>17.8±12.01</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>supernatant without stimulation</td>
<td>13.7±3.26</td>
<td>11.3±0.00</td>
<td>10.2±0.07</td>
<td>5.4±0.00</td>
<td>0.027</td>
<td>0.1±0.05</td>
<td>0.12</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Serum</td>
<td>149.7±24.54</td>
<td>76.75±48.94</td>
<td>51.5±24.44</td>
<td>55.25±5.30</td>
<td>0.003</td>
<td>46.6±27.93</td>
<td>0.012</td>
</tr>
<tr>
<td></td>
<td>supernatant stimulated with PHA</td>
<td>145.7±45.77</td>
<td>103.25±38.15</td>
<td>95.0±7.07</td>
<td>80.0±28.28</td>
<td>0.027</td>
<td>61.9±19.79</td>
<td>0.049</td>
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<td>supernatant without stimulation</td>
<td>79.3±37.20</td>
<td>3.05±2.75</td>
<td>0.060±0.00</td>
<td>0.06±0.00</td>
<td>0.342</td>
<td>0.0±0.00</td>
<td>0.98</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>Serum</td>
<td>467.1±15.05</td>
<td>825.5±144.85</td>
<td>983.0±212.09</td>
<td>995±353.55</td>
<td>0.432</td>
<td>990±291.05</td>
<td>0.25</td>
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<td></td>
<td>supernatant stimulated with PHA</td>
<td>401.087±204.57</td>
<td>687.37±89.50</td>
<td>700.0±70.10</td>
<td>730.0±275.7</td>
<td>0.489</td>
<td>563.40±100.0</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>supernatant without stimulation</td>
<td>131.7±60.12</td>
<td>5.5±1.29</td>
<td>6.0±5.56</td>
<td>2.0±1.00</td>
<td>0.06</td>
<td>0.0±0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

* mean ±SD.
 a: The difference between pre- and post-treatment is significant (P < 0.05).
 b: The difference between pre- and post-treatment is non significant (P > 0.05).
 c: The difference between control and CHB patients is highly significant (P < 0.05).
 d: There is no significant difference between CHB patients and control (P > 0.05).

Kakumu et al.[17] reported that CHB patients who received IFN- α2b and 1L-2 therapies showed depressed IL-6 activity during treatment, and rebound beyond pre-treatment values after cessation of therapy. These findings suggest that IL-6 plays a role in the development of CHB, and it may contribute, at least in part, to the elimination of HBV.

The present study also showed no significant difference of IL-6 levels pg/ml in CHC patients that shown in table(2), as compared to their levels in healthy controls both in vivo and in vitro (P < 0.05). Also this study showed that there was significant difference of IL-6 levels between pre- and post-treated CHC patients in vivo and in vitro (stimulated with PHA) (P < 0.05). This difference may be due to the effectiveness of IFN- α treatment as Quadri et al.[18] reported that serum IL-6 concentration was initially elevated in chronic HCV, increased level was detected before IFN- α therapy followed by decreased level after 6th IFN- α dose.

Ren et al., [19] showed a significant increase in IL-6 levels in patients with HCV as compared with healthy control. Falasca et al., [20]
found that HCV positive and HBV positive patients have higher levels of Th2 cytokines, particularly in the course of CHB, and that IL-8 and IL-6 levels may have important roles as markers of both inflammation and hepatic injury particularly in the course of HC.

2- Level of IL-10

In the present study, there was an increased levels of IL-10 (Pg/ml) was observed in patients with CHB infection pre-treatment, as compared to their levels in healthy control (P < 0.0001) both in vivo and in vitro (with and without stimulation by PHA). Also this study showed that there was a highly significant difference in IL-10 levels between pre-and post-treatment (p < 0.05) (table 1). These results were coincided with other results of Vingerhoets et al.[21]; Hsu et al.[2] who reported that the levels of IL-10 in CHB patients were recorded a significant elevation as compared with healthy control.

Also the present study showed that there was significant difference of IL-10 levels (Pg/ml) in CHC patients pre-treatment as compared to their levels in healthy controls both in vivo and in vitro (with stimulation by PHA) (P <0.05) (table 2). In addition, this study showed a significant difference in IL-10 levels between pre- and post-treated CHC patients in vivo and in vitro(with and without stimulation by PHA) (P < 0.05) (table 2). These results coincided with the results of Abayi et al.[22].

Kakuma et al.[23] reported that the levels of IL-10, and IL-2 secreted by PBMCs taken from chronically infected patients with HCV were significantly elevated than in control group. Radkowski et al.[24] found that IL-10 concentration was higher in supernatant from infected macrophages stimulated by PHA, but this difference didn't reach statistical significance(P< 0.05).

### Table (2): Comparison of cytokine levels between (40) pre- and (27) post-treated CHC patients in vivo and in vitro.

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Source</th>
<th>Pre-treatment* (40)</th>
<th>Post-treatment* (27)</th>
<th>P Value</th>
<th>Control (15)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ribovirin(6)</td>
<td>IFN-α2(13)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>±10±1.25</td>
<td>±10±1.25</td>
<td>0.014*</td>
<td>38.83±27.65</td>
<td>0.2</td>
</tr>
<tr>
<td>IL-6</td>
<td>Serum</td>
<td>197.38±10.25</td>
<td>126.66±36.71</td>
<td>0.014*</td>
<td>38.83±27.65</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>±10±1.25</td>
<td>±10±1.25</td>
<td>0.014*</td>
<td>38.83±27.65</td>
<td>0.2</td>
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<tr>
<td></td>
<td></td>
<td>69.33±0.34</td>
<td>62.72±52.01</td>
<td>0.005*</td>
<td>42.07±10.60</td>
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<td></td>
<td></td>
<td>±10±1.25</td>
<td>±10±1.25</td>
<td>0.017*</td>
<td>-</td>
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<tr>
<td></td>
<td></td>
<td>0.35±0.43</td>
<td>0.54±0.10</td>
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<tr>
<td>IL-6</td>
<td>Serum</td>
<td>211.69±52.42</td>
<td>27.92±31.84</td>
<td>0.017*</td>
<td>18.63±16.02</td>
<td>0.006*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>±10±1.25</td>
<td>±10±1.25</td>
<td>0.017*</td>
<td>18.63±16.02</td>
<td>0.006*</td>
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<td>43.33±22.32</td>
<td>31.61±18.26</td>
<td>0.030*</td>
<td>17.86±12.01</td>
<td>0.006*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>±10±1.25</td>
<td>±10±1.25</td>
<td>0.42*</td>
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<td>15.05±1.14</td>
<td>1.0±1.14</td>
<td>0.030*</td>
<td>17.86±12.01</td>
<td>0.006*</td>
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<tr>
<td></td>
<td></td>
<td>±10±1.25</td>
<td>±10±1.25</td>
<td>0.42*</td>
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<tr>
<td>TNF-α</td>
<td>Serum</td>
<td>147.15±26.28</td>
<td>27.92±31.84</td>
<td>0.030*</td>
<td>46.05±27.93</td>
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<td>±10±1.25</td>
<td>±10±1.25</td>
<td>0.030*</td>
<td>46.05±27.93</td>
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<td>83.53±14.4</td>
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<td>IFN-γ</td>
<td>Serum</td>
<td>131.15±52.87</td>
<td>102.79±48.10</td>
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<td>61.93±19.70</td>
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<td>0.42*</td>
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<td>1.55±0.10</td>
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<td></td>
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<td>0.65±0.49</td>
<td>0.1±0.14</td>
<td>0.030*</td>
<td>17.86±12.01</td>
<td>0.006*</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>Serum</td>
<td>445.35±349</td>
<td>519.23±720.83</td>
<td>0.21*</td>
<td>75.9±207.11</td>
<td>0.3</td>
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<td></td>
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<td>±10±1.25</td>
<td>±10±1.25</td>
<td>0.21*</td>
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<td></td>
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<td>685.33±488.99</td>
<td>723.15±500.70</td>
<td>0.002*</td>
<td>-</td>
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<tr>
<td></td>
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<td>±10±1.25</td>
<td>±10±1.25</td>
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<td>755.33±282.01</td>
<td>300.70±500.70</td>
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<td>±10±1.25</td>
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<td>10±4.34</td>
<td>75±69.05</td>
<td>0.062*</td>
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<td>±10±1.25</td>
<td>0.062*</td>
<td>-</td>
<td>-</td>
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</table>

* mean ±SD.
a: The difference between pre- and post-treatment is highly significant (P < 0.05).
b: The difference between pre- and post-treatment is non-significant (P < 0.05).
c: The difference between CHC patient and control is significant (P < 0.05).
d: The difference between CHC patient and control is non-significant (P < 0.05)
3-Level of Tumor Necrosis Factor – α (TNF – α)
In the present study there was an increased level of TNF – α in CHB patient’s pre – treatment as compared with control subjects with significant differences ( p < 0.05 ) (table 1) both in vivo and in vitro (supernatant of PB MCs stimulated by PHA). Also there was significant differences ( p < 0.05 ) of TNF – α levels between pre and post treated CHB patients in vivo and in vitro (supernatant of PB MCs stimulated by PHA but not without stimulation) (table 1). These results are in agreement with other results of (2,3) who reported that in response to HBV infection a broad range of proinflammatory cytokines and chemokines which required for viral clearance were produced, such as IL – 1β, IL – 6, IL – 8, IL – 12, TNF – α and IFN – γ.
In addition, in the present study there was an increased levels of TNF – α in CHC patients, as compared with the control group but with no significant differences ( p < 0.05 ) (table 2) both in vivo and in vitro (PBMCs stimulated by PHA). Also there was a significant difference of TNF – α levels (pg / ml) between pre – and post – treated CHC patients in vivo and in vitro (PBMCs stimulated by PHA but not that were without stimulation (table 2) (p< 0.05). This result coincided with the result of Hsu et al[2].
Radkowski et al[24] found that exposure of primary macrophage to HCV positive sera (before treatment with IFN- α2b) resulted in enhanced production of TNF – α and IL – 8 and their respective mRNA.

4 - Levels of Interferon – γ (IFN– γ)
The results of this study showed the decreased of IFN – γ levels( pg/ml) of CHB patients pre-treatment ; and no significant difference has been shown between this patients and control and between pre – and post – treated patients (table 1) both in vivo and in vitro (with and without stimulation by PHA).

This result is in agreement with Livingston et al[16] who reported that the secretion of the Th 1 – associated cytokine IL – 12 and IFN – γ were considerably reduced in patients with CHB infection compared to normal subjects , while secretion of Th2 cytokine IL – 5 appeared to be elevated , although not significantly . Also they showed that the secretion of IFN – γ in supernatant of PBMCs from CHB patients (that stimulated by PHA as a mitogen stimulus) was decreased in PBMCs supernatant in comparison to normal subjects.

In addition, in this study the IFN – γ estimation showed decreased level in mean ± SD( pg / ml ) in CHC patients with no significant difference as compared with control in vivo and in vitro (stimulated by PHA) (table 2) and between pre – and post – treated CHC patients in vivo ( p < 0.05 ). While in comparison with in vitro (supernatant of PBMCs stimulated by PHA) showed significant difference between pre – and post – treated CHC (p< 0.05).

This result is in agreement with Abayli et al[22] who studied the serum profile of Th1 and Th2 cytokines, in chronically HCV infected patients and found that the Th2 cytokines were increased remarkably include IL – 10, IL – 4, while the Th1 cytokine IFN – γ revealed no difference and they suggested that Th1 response decreased during CHC infection.

References:


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قياس الاستجابة المناعية الخلوية من خلال تقييم بعض السايتوكينات في المرضى العراقيين المتعتين مناعيا والمصابين بالتهاب الكبد الفيبروسي نمط B و ج و في العلاج (داخل وخارج الجسم الحي).”

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الكلمات المفتاحية: الاستجابة المناعية الخلوية، السايتوكينات، التهاب الكبد الفيبروسي، نمط B، التهاب الكبد الفيبروسي، نمط ج

الخلاصة:

تم تبني هذه الدراسة لغرض تقييم بعض السمات السريرية والمناعية والفيبروسية لدى المرضى العراقيين المتعتين بالتهاب الكبد الفيبروسي المزمن نمط B (ج) وتحديد مدى استجابة العلاج بفئتي الانتقائي، اللافينودين، والترترافين.

مجمعات من المرضى المصابين بالتهاب الكبد الفيبروسي المزمن تم تصنيفهم إلى مجموعتين رئيسية: مجموعة المرضى قبل العلاج وتضمنت (25) مريضا مصابا بالتهاب الكبد الفيبروسي المزمن نمط (ب) والذين اظهروا نتائج موجبة لفحص المستضد المناعي لفأربوركس الكبد نمط (ب) و(الذين رفعت الدهون 6 شهر) ومجموعة المرضى بعد العلاج وتضمنت (12) مريضا مصابا بالتهاب الكبد الفيبروسي المزمن نمط (ج) و(الذين رفعت الدهون 6 شهر) وعلاجم اعتبرنا نتائجهم مفيدة.

الترترافين، اللافينودين وانتقائيات الفيبروسية، وانتقائيات الفيبروسية المزمن نمط (ج) و(الذين رفعت الدهون 6 شهر) وعلاجم اعتبرنا نتائجهم مفيدة.

بالاعتماد على نتائج الاستجابة المناعية، استخدمت فئتي الانتقائي، اللافينودين، والترترافين، و(الذين رفعت الدهون 6 شهر) في فئتي الانتقائي، اللافينودين، والترترافين، و(الذين رفعت الدهون 6 شهر) في فئتي الانتقائي، اللافينودين، والترترافين، و(الذين رفعت الدهون 6 شهر) في فئتي الانتقائي، اللافينودين، والترترافين، و(الذين رفعت الدهون 6 شهر) في فئتي الانتقائي، اللافينودين، والترترافين، و(الذين رفعت الدهون 6 شهر) في فئتي الانتقائي، اللافينودين، والترترافين، و(الذين رفعت الدهون 6 شهر) في فئتي الانتقائي، اللافينودين، والترترافين، و(الذين رفعت الدهون 6 شهر) في فئتي الانتقائي، اللافينودين، والترترافين، و(الذين رفعت الدهون 6 شهر) في فئتي الانتقائي، اللافينودين، والترترافين، و(الذين رفعت الدهون 6 شهر) في فئتي الانتقائي، اللافينودين، والترترافين، و(الذين رفعت الدهون 6 شهر) في فئتي الانتقائي، اللافينودين، والترترافين، و(الذين رفعت الدهون 6 شهر) في فئتي الانتقائي، اللافينودين، والترترافين، و(الذين رفعت الدهون 6 شهر) في فئتي الانتقائي، اللافينودين، والترترافين، و(الذين رفعت الدهون 6 شهر) في فئتي الانتقائي، اللافينودين، والترترافين، و(الذين رفعت الدهون 6 شهر) في فئتي الانتقائي، اللافينودين، والترترافين، و(الذين رفعت الدهون 6 شهر) في فئتي الانتقائي، اللافينودين، والترترافين، و(الذين رفعت الدهون 6 شهر) في فئتي الانتقائي، اللافينودين، والترترافين، و(الذين رفعت الدهون 6 شهر) في فئتي الانتقائي، اللافينودين، والترترافين، و(الذين رفعت الدهون 6 شهر) في فئتي الانتقائي، اللافينودين، والترترافين، و(الذين رفعت الدهون 6 شهر) في فئتي الانتقائي، اللافينودين، والترترافين، و(الذين رفعت الدهون 6 شهر) في فئتي الانتقائي، اللافينودين، والترترافين، و(الذين رفعت الدهون 6 شهر) في فئتي الانتقائي، اللافينودين، والترترافين، و(الذين رفعت الدهون 6 شهر) في فئتي الانتقائي، اللافينودين، والترترافين، و(الذين رفعت الدهون 6 شهر) في فئتي الانتقائي، اللافينودين، والترترافين، و(الذين رفعت الدهون 6 شهر) في فئتي الانتقائي، اللافينودين، والترترافين، و(الذين رفعت الدهون 6 شهر) في فئتي الانتقائي، اللافينودين، والترترافين، و(الذين رفعت الدهون 6 شهر) في فئتي الانتقائي، اللافينودين، والترترافين، و(الذين رفعت الدهون 6 شهر) في فئتي الانتقائي، اللافينودين، والترترافين، و(الذين رفعت الدهون 6 شهر) في فئتي الانتقائي، اللافينودين، والترترافين، و(الذين رفعت الدهون 6 شهر) في فئتي الانتقائي، اللافينودين، والترترافين، و(الذين رفعت الدهون 6 شهر) في فئتي الانتقائي، اللافينودين، والترترافين، و(الذين رفعت الدهون 6 شهر) في فئتي الانتقائي، اللافينودين، والترترافين، و(الذين رفعت الدهون 6 شهر) في فئتي الانتقائي، اللافينودين، والترترافين، و(الذين رفعت الدهون 6 شهر) في فئتي الانتقائي، اللافينودين، والترترافين، و(الذين رفعت الدهون 6 شهر) في فئتي الانتقائي، اللافينودين، والترترافين، و(الذين رفعت الدهون 6 شهر) في فئتي الانتقائي، اللافينودين، والترترافين، و(الذين رفعت الدهون 6 شهر) في فئتي الانتقائي، اللافينودين، والترترافين، و(الذين رفعت الدهون 6 شهر) في فئتي الانتقائي، اللافينودين، والترترافين، و(الذين رفعت الدهون 6 شهر) في فئتي الانتقائي، اللافينودين، والترترافين، و(الذين رفعت الدهون 6 شهر) في فئتي الانتقائي، اللافينودين، والترترافين، و(الذين رفعت الدهون 6 متر)