ISSN: 0975 -8542

Journal of Global Pharma Technology
Available Online at: www.jgpt.co.in

RESEARCH ARTICLE

Correlation of IL-10 Gene Polymorphisms and Serum Level with Hepatitis C Virus Infection in Iraq

Nawar B. Abdulsahib, Hassan M. Naif*

Department of Molecular and Medical Biotechnology, College of Biotechnology, Al-Nahrain University, Baghdad, Iraq.

***Corresponding Author: Hassan M Naif**

Abstract

Hepatitis C virus (HCV) infection is a major health problem worldwide where130-150 million people are chronically infected with HCV, which progress to cirrhosis or hepatocellular carcinoma. A total of 120 subjects were recruited to assess the correlation between gene polymorphisms (IL-10-1082 and -819) with the susceptibility to HCV infection in Iraqi patients by using allele specific PCR. The serum level of IL-10 was assessed by ELISA. Gene polymorphism results of IL-10-1082A/G (rs1800896) showed significant increase in AA distribution (P=0.0076) and allele A frequency (P=0.049) among the control group while AG distribution were significantly higher in patients (P=0.0082). Although, G allele frequency had but an association (P=0.049), but the homozygous GG mutant genotype had no significant differences between the two groups. While the genotype analysis of the second SNPs of IL-10-819C/T (rs1800872) showed that neither CC nor CT genotypes distribution were associated with HCV infection (0.1627 and 0.2559, respectively) but the TT distribution and allele frequency had a suggestive association in patients (P=0.0483 and 0.0257, respectively). Results of IL-10 serum levels were higher by two-fold in patients than in healthy controls. It appeared that the IL-10-1082 AA genotype had a protective effect against HCV infection but the TT genotype of -819 mutations had a suggestive association with susceptibility to infection with HCV in Iraqi patients. Such correlation may indicate a protective role for IL-10 and could be used as a predictive risk susceptibility biomarker for progressive infection with HCV.

Keywords: *Hepatitis C virus, IL-10, Polymorphism, Cytokine, Iraq.*

Introduction

Hepatitis C virus (HCV) infection is a major health problem worldwide. Chronic HCV infection commonly induces immune reactive inflammation, which results in continuous liver tissue damage and progression of liver fibrosis to cirrhosis or hepatocellular carcinoma. Viral genotyping and identification of certain gene sequences assist into HCV classification [1].It is known that different genotypes respond differently to medication and dictate the vaccine choice.

Currently, six major genotypes and more than 80 subtypes have been identified from around the world [2, 1]. Several risk factors have been associated with identifying patients who were exposed to HCV infection with a favorable outcome. Genetic differences among the infected hosts can determine the progression of the infection and disease outcome, causing different individuals to respond in different ways to the viral infection [3]. The correlation between single-nucleotide polymorphisms (SNPs) and serum levels were associated with disease course in patients with HCV infection [4, 5]. Cytokines play an immunoregulatory role in infection and inflammatory disease which may contribute to imbalance of the inflammatory profile of the patient and affects the clinical outcome and the severity of HCV [6].

In HCV infection, IL-10 appeared to interfere with the progression of disease, viral persistence and the response to therapy [7]. The genetic polymorphism of IL-10 promoter gene has a definitive but inconclusive effect on HCV infection as determined by the presence of three SNPs and haplotype in its promoter [8].

Patients and Methods

©2009-2020, JGPT. All Rights Reserved

Subjects

Sixty patients were used after confirmation that they were infected with HCV. Diagnosis was done by consultant based on clinical examination and blood screening test for HCV antibodies. Family unrelated apparently healthy 60 individuals from different locations in Baghdad were selected to represent the control group. The mean ages of patients and control were 36 ± 14 and 35 ± 16, respectively. Informed consents were taken from patients as well as controls which included individual's clinical, personals characteristic and type of treatment.

Sample Collection

From each individual included in this study, 5-10 ml of blood sample was drawn by vein puncture using disposable syringes. The blood for each patient was divided into two tubes; one was used for DNA extraction and the other one for serum purification. Sera were separated by centrifugation for 5 minutes at 3000 round revolution per minute (rpm), and divided into aliquots of (250 µl) to be used for measuring IL-10 cytokine levels.

DNA Extraction and PCR Amplification of IL-10 gene Polymorphism

DNA was extracted using commercial kit (DNA Mini Kit Whole Blood Protocol, Gene aid, Korea). IL-10 serum level was assessed using commercial available kit (Komabiotec, Korea). Extracted DNA from blood samples was used in PCR for amplification and detection of IL-10 gene polymorphisms [9]. PCR amplification reactions containing an antisense generic primer and a sense allele-specific primer were performed for each IL-10 polymorphism.

The primers used in this study were antisense generic primer (5'-CAGTGCCAACTGAGAATTTGG-3') and a sense allele-specific primer (5'-ACTACTAAGGCTTCTTTGGGAA-3') and a specific mutant primer (5'-CTACTAAGGCTTCTTTGGGAG-3') for the SNP -1082 (G/A). While for amplification of IL-10-819 SNP, antisense generic primer (5'-AGG ATGTGTTCCAGGCTCCT-3') and a sense allele-specific primer (5'-ACCCTTGTACAG GTGATGTAAT-3') and a specific mutant primer (5'-CCCTTGTACAGGTGATGTAAC-3') were used. All volumes of the PCR reaction mixture were completed to 25µL using nuclease free water. In all amplification experiments, a negative blank control (which contained all PCR materials except the target DNA) was included. The Go Taq® Green Master Mix was thawed at room temperature and was mixed by vertexing then it was spun briefly in a micro centrifuge. The Go Taq® Master Mix (Promega) containing Taq polymerase 2.5 µL, dNTP 250 µM, Tris-base (pH 9.0) 10 mM, KCl 30 mM and MgCl2 1.5 mM.

PCR reaction used to amplify IL-10 gene polymorphism was composed of 12.5µL of IX Go Taq® Green Master Mix, 0.2 µL of 20 pmol concentrations from each primer, 3 µL of template DNA and nuclease free water 9.1µL. The cycling conditions for amplification of IL-10 -1082 genotypes were as follows: 5 min at 94˚C, followed by 35 cycles of 94˚C for 1min, 60˚C for 1 min. and 72˚C for 1 min, and a final extension of 10 min at 72˚C, the sizes of the fragments were 258 bp. The same cycling conditions were used for IL-10 -819 genotypes except the annealing step was on 59˚C instead of 60˚C for IL-10 -1082 the sizes of the fragments were 233 bp.

Statistical Analysis

The one-way analysis of variance ANOVA (Duncan), *t*-test and Chi Square were performed to study effect of different factors in the study parameters and to test whether group variance was significant or not. Statistical significance was defined as $p \leq 0.05$. Data were expressed as mean ± standard deviation and statistical significance were carried out using Graph Pad Prism version 6 (Graph Pad Software Inc., La Jolla, CA, USA).

Results

Detection of gene Polymorphisms of IL-10-1082A/G (rs1800896) and -819C/T (rs3021097) by allele specific PCR

Results of amplification of IL-10-1082A/G (rs1800896) by using allele specific (AS) PCR, revealed a specific amplicon with a molecular size of 258 bp in both HCV patients and controls (Figure 1).

©2009-2020, JGPT. All Rights Reserved

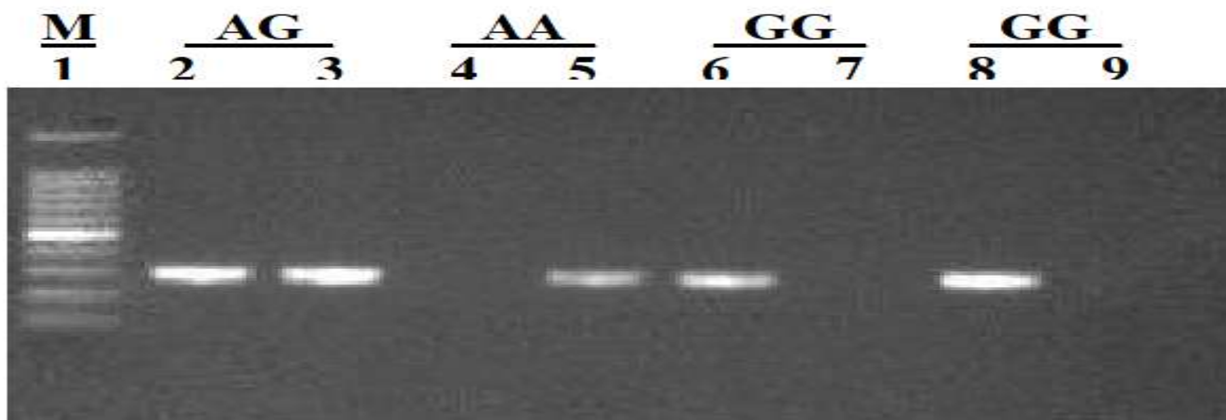

Figure 1: Genotype distribution of IL-10 (-1082A/G) in HCV infected patients by using allele-specific PCR. Amplicons electrophoresed on a 2% agarose gel stained with ethidium bromide and then visualized under a UV transilluminator and photographed. The 258 bp DNA bands represent the amplification of IL-10- 1082A/G. Lanes order: lane 1 (M), 100 bp DNA marker; lanes 2-3, AG; lanes 4-5, AA and lanes 6-7, 8-9, GG genotype

Genotyping results of IL-10-1082A/G (rs1800896) in both HCV-infected patients and healthy controls had three genotypes: AA, AG, and GG (data will be presented in that order. In HCV patients, the distribution of these genotypes were 16 (26.6%), 35 (58.4%), and 9 (15%), respectively; while in healthy controls were 28 (46.6%), 24 (40%), and 8 (13.4%), respectively. The statistical analysis of genotypes and alleles frequencies related to this polymorphism revealed a significant increase in the AA genotypes of healthy group (P=0.0076) (OR, 95%CI, 1.258 (0.79-1.58). The A allele appeared also at a significant ratio among healthy individuals (P=0.049). Conversely, the heterozygous AG mutant genotype showed an elevated frequency in HCV patients (P=0.009) (OR, 95%CI, 1.065 (0.82-1.49). While the homozygous GG frequency had no significant differences between the two study groups (P=0.644) (Table 1). However, allele frequencies of C was significantly appeared in patients (P=0.049).

Table 1: Genotypes and allele frequencies of IL-10-1082A/G (rs1800896) in HCV infected patients (cases) and in uninfected healthy individuals (controls)

Genotype	Cases (N=60)	Control (N=60)	P-value	OR (95%CI)
AA	16 (26.6%)	28 (46.6%)	0.0076 **	1.258 (0.79-1.58)
AG	35 (58.4%)	24 (40%)	0.0082 **	1.065 (0.82-1.49)
GG	9 (15%)	8 (13.4%)	0.644 NS	0.367 (0.28-0.51)
Allele frequency				
A	0.56	0.66	0.049 *	0.663 (0.74-1.49)
G	0.44	0.34	0.049 *	0.663 (0.72-1.44)

* (P<0.05), ** (P<0.01)

When the genotypes distribution were associated with treated vs untreated HCV infected patients used in this study, AG distribution, again, showed significant distribution in treated but not in untreated patients, but not as such for the GG or AA distribution (Table 2). Antiviral treatment obviously did not change the pattern of genotype distribution but lessen the difference in allele frequency of being insignificant.

Table 2: Distribution of IL-10-1082A/G (rs1800896) genotype and allele frequencies in treated and untreated patients infected with HCV

Genotype	Treated patients (N=30)	Untreated patient (N=30)	P-value	OR (95%CI)
AA	6 (20%)	10 (33.4%)	0.094 NS	0.394 (0.88-1.65)
AG	21 (70%)	14 (46.6%)	0.0035 **	1.347 (0.86-1.63)
GG	3 (10%)	6 (20 %)	0.049 *	0.638 (0.88-1.62)
Allele frequency				
A	0.55	0.56	0.062 NS	---
G	0.45	0.44	0.062 NS	---

* (P<0.05), ** (P<0.01), NS: Non-Significant.

©2009-2020, JGPT. All Rights Reserved

The second variant of IL-10 -819C/T (rs3021097) was amplified by AS-PCR for all patients and control individuals and results showed a specific amplicon with a molecular size of 233 bp in both HCV patients and controls (Figure 2).

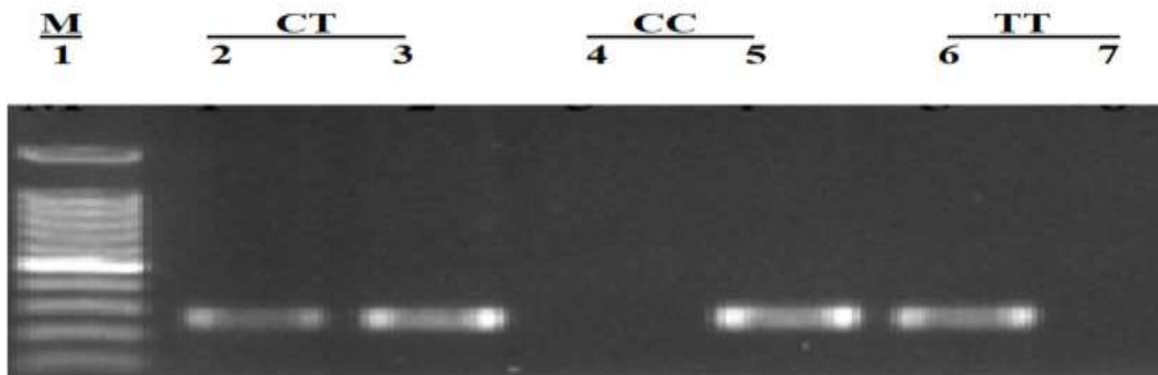

Figure 2: Genotype distribution of IL-10 -819C/T (rs3021097) genotypes' distribution in HCV infected patients and healthy controls by using allele-specific (AS) PCR. Experimental conditions were similar to those described in Figure 1. The 233 bp represents the amplification of IL-10-819C/T variants. Lanes order: lanes 1- 2, CT; lanes 3-4, CC; lanes 5-6, TT genotype and lane M; 100 bp DNA marker

The genotype analysis of IL-10-819C/T (rs1800872) in both HCV infected patients and uninfected healthy controls displayed three genotypes: CC, CT, and TT. They appeared in 8 (16.6%), 38 (61.8%) and 14 (21.6%) of HCV infected patients, respectively; whereas they appeared in 14 (23.4%), 40 (66.6%) and 6 (10%) of healthy controls, respectively (Table 2). In contrast to the homozygous CC wild genotype which showed a significant increase in patients (P=0.0483; OR, 0.773; 95%CI, 0.61-1.04), the distribution frequencies of homozygous TT and heterozygous CT did not show significant differences between patients and controls (P=0.2559; OR, 0.309; 95%CI, 0.18-0.46 and P=0.1627; OR, 0.386; 95%CI=0.31-0.58, respectively).

Table 3: Distribution of IL-10-819C/T genotypes and allele frequencies in HCV infected patients (cases) and in uninfected healthy controls

Genotype	Cases (N=60)	Control (N=60)	P-value	OR (95%CI)
CC	8 (16.6%)	14 (23.4%)	0.1627 NS	0.386 (0.31-0.58)
CT	38 (61.8%)	40 (66.6%)	0.2559 NS	0.309 (0.18-0.46)
TT	14 (21.6%)	6 (10%)	0.0483 *	0.773 (0.61-1.04)
Allele frequency				
C	0.45	0.60	0.0257 *	0.773 (0.58-1.11)
T	0.55	0.40	0.0257 *	0.773 (0.58-1.08)

***** (P<0.05), NS: Non-Significant.

Antiviral treatment influence on the genotype and allele frequencies in the same cohort of infected patients revealed similar pattern of genotype distribution as seen in Table 3 but the differential allele frequency was disappeared (Table 4).

Table 4: Distribution of IL-10 -819 C/T genotype and allele frequencies in treated and untreated patients infected with HCV

Genotype	Treated patients (N=30)	Untreated patient (N=30)	P-value	OR (95%CI)
CC	6 (20%)	8 (26.8%)	0.089 NS	0.476 (0.87-1.61)
TC	18 (60%)	20 (66.6%)	0.084 NS	0.478 (0.92-1.61)
TT	6 (20%)	2 (6.6%)	0.027 *	0.792 (0.88-1.58)
Allele frequency				
C	0.50	0.40	0.430 NS	—
T	0.50	0.60	0.430 NS	—

***** (P<0.05), NS: Non-Significant

©2009-2020, JGPT. All Rights Reserved

Circulating IL-10 in HCV Infected Patients and Healthy Controls

Results showed that the mean levels of IL-10 in the sera from HCV patients were higher (17.3 pg/ml) than that observed in the control group (13.8 pg/ml) (Figure 3).

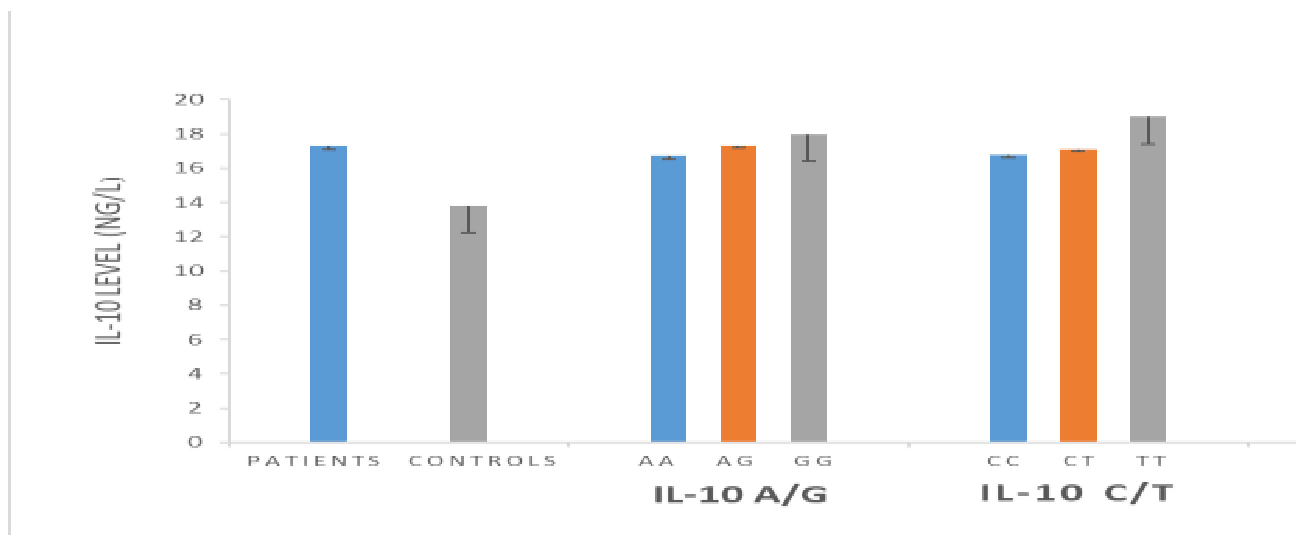

Figure 3: IL-10 serum levels in HCV infected patients and controls as measured by an ELISA serological assay using a commercially available kit (Human Interleukin 10 ELISA Kit, Komabiotec, Korea)

When the IL-10 levels were correlated with the three genotypes AA, AG and GG of IL-10-1082A/G polymorphism in HCV patients, results showed that patients with the homozygous mutant GG genotypes had the highest levels of IL-10 (18.08 ± 3.97pg/ml), followed by the heterozygous AG genotypes (17.30 ± 3.11 pg/ml) and the AA genotypes ended up with the lowest levels of IL-10 (16.74 ± 1.54pg/ml) (Figure 3). However, these differences were not significant.

Regarding the correlation between the other IL-10 (-819C/T) polymorphic genotypes (CC, CT and TT) and cytokine level in HCV infected patients. It was revealed that patients with the wild-type homozygous CC genotype had the lowest level of IL-10 (16.86 ± 1.74 pg/ml) in blood. While the heterozygous CT had an intermediate level of IL-10 (17.13 ± 2.80pg/ml) but the homozygous TT genotype showed the highest level (19.05 ± 4.96pg/ml) (Figure 3).

Discussion

In this study, after developing a successful allele-specific-PCR for detection of IL-10 gene polymorphisms (-1082 and -819) was specifically amplified and analyzed in both HCV infected patients and controls. In general, all samples tested for the two SNPs of the two experimental groups exhibited three genotype distribution represented the homozygous wild, heterozygous mutant, and homozygous mutant genotypes but at variable ratios.

The distributions of all genotypes were fit to Hardy Weinberg Equilibrium (HWE) in examined experimental groups. Gene polymorphism results of IL-10-1082A/G (rs1800896) in both HCV-infected patients and healthy controls had three genotypes: AA, AG, and GG. There were significant differences between patients and controls for both homozygous AA wild genotype (P=0.008) in the control group, and for the heterozygous AG genotype (P=0.009) in HCV infected patients.

The homozygous mutant GG alleles showed no significant differences between the two groups. In this study, IL-10-1082 genotype distribution was paradoxical where AA genotype was seen more frequently in the control group with no association with risk to HCV infection while the AG distribution was more in patients. This paradox was also reflected at the A and G allele frequency levels.

Our findings were similar to those reported earlier [10]. On the other hand, others found that GG genotype is linked to a higher risk of HCV infection [11, 12]. The AG polymorphism was also reported to be associated with higher HCV infection rates in the USA [13] but not in Japan [14], Tunisia [15], Italy [16], and in China [17].Such controversial findings may be attributed to ethnicity and races play a role in such variability. The third factor could be attributed to the stage of HCV disease,

©2009-2020, JGPT. All Rights Reserved

particularly with GG genotype which was associated with viral clearance [18] or persistent infection [19]. The fourth factor could be the difference in sample size used in these studies. In general, the IL-10 circulating levels in patients was higher than controls but no definitive association between IL-10-1082 genotypes and the serum levels of IL-10 production. Although there was an increase of IL-10 secretion levels in those with GG genotypes which may indicate its role in immune response to the virus.

The latter was also observed by Afzal et al., [9] and Reuses *et al.*, [20].While the genotype analysis of IL-10-819C/T (rs1800872) in both HCV infected patients and uninfected healthy controls also displayed three genotypes: CC, CT, and TT with the TT distribution was greater in patients (P=0.044) while CT and CC did not show significant differences between patients and controls but higher (60%) at the allele level in uninfected individuals. These data suggested that CC had a protective role against HCV infection. Similar findings came also from Iran [21].

The pathogenesis of chronic HCV infection is not well understood, but the vigor of T cell response to HCV antigens is one of the most important factors capable of influencing disease outcome. During hepatitis C virus infection, humoral and cell-mediated immune responses play a key role in the host defense. However, the crucial role of T cell response is often unable to control viral replication. In fact, functional T cell exhaustion with impaired proliferative potential and altered cytokine production can occur, leading to persistent viral infection [22]. IL-10 plays an anti-inflammatory role in the immune system because it inhibits the production of pro-inflammatory cytokines and limits T cell activation and differentiation [23].

Due to its immunoregulatory action, it has been assumed that inadequate levels of IL-10 can determine long-term escape of pathogens from immune control and give rise to persistent infections [24]. During HCV infection, the levels of circulating certain cytokines are usually associated with virus persistence and/or failure of antiviral therapy [25, 26]. In this study, serum levels of IL-10 values were higher in HCV patients compared to healthy controls. The higher serum levels may serve as additional biomarker to monitor persistence and disease progression.

In conclusion, only the wild type genotypes and to some extent the heterozygote genotype of both IL-10 gene polymorphisms (IL-10-1082 and -819) but the mutant genotypes had no effect on risk of HCV infection in local patients. These data suggest that IL-10 -1082 and -819 mutations had no significant correlation with HCV infection indicating a protective role for IL-10 where the circulating levels of IL-10 were shown to be higher in HCV infected patients[7].

References

1. Simmonds P, Bukh J, Combet C, Deleage G, Enomoto N, Feinstone S (2005) Consensus proposals for a unified system of nomenclature of hepatitis C virus genotypes. Hepatology, 43: 962-973.
2. Kuiken C, Simmonds P (2009) Nomenclature and numbering of the hepatitis C virus. Methods Mol. Biol., 2 (510): 33-53.
3. Bei Z, Cuiyu W, Xiaoli Z, Juan H, Jianqing W, Rongbin Y, Weihong Z (2015) Relationships between interleukin-12B and interleukin-10 gene polymorphisms and hepatitis C in Chinese Han hemodialysis patients. Journal Renal Failure, 37: 3.
4. Elemshaty H, Nasef W, Mohamed I (2015) Serum Cytokine of IL-10 and IL-12 in Chronic Liver Disease: The Immune and Inflammatory Response. Disease Markers, 1-7.
5. Timothy L M, Priya D, James J G, Gregory D K, Keith H, Leslie H T, Michael B, Marion G P, Hugo R R, David L T, Chloe L (2010) Large-Scale Candidate Gene Analysis of Spontaneous Clearance of Hepatitis C Virus. Journal of Infectious Diseases, 201 (9): 1371-1380.
6. Julia d I, Angela C, Karen F, Dermot K, Margalida R, Jacques F, Raquel M, Sara P, Hansjakob F, Huldrych F G, Manuel B, Enos B, Patrick S, Bernard H, Eleanor B, Paul K, Amalio T, Andri R, Swiss (2011) HIV Cohort Study Estimating the Net Contribution of Interleukin-28BVariation to Spontaneous Hepatitis C Virus Clearance. Hepatology, 53: 5.
7. Naylê M, Fabiana N, Beatris M, Ricardo d, Deise M, Rubens L, Maria B (2015)

©2009-2020, JGPT. All Rights Reserved

Polymorphisms of IL-10 gene in patients infected with HCV under antiviral treatment in southern Brazil. Cytokine, 73 (2): 253-257.

8. Yanhua L, Jiuping W, Juan W, Yunfeng X, Bin X, Hongwei L, Liu Y, Xiaoke H, Yueyun M (2017) SVR Rates of HCV-infected population under PEG-IFN-α/R treatment in Northwest China. Virology Journal, 14: 62.
9. Afzal MS, Tahir S, Salman A (2011) Analysis of interleukin-10 gene polymorphisms and hepatitis C susceptibility in Pakistan. J. Infect Dev. Countries, 5: 473-9.
10. Li J, Liu Y, Xu F, Chen J, Chen Y (2013) Three polymorphisms in the IL-10 gene and the risk of HCV infection: a meta-analysis plus a Chinese Association Study involving 1140 subjects. Epidemiol Infect, 141(5): 893-904.
11. Gao Q, Zhang S, Wu L, Jia M, Mi Y, Liu D (2011) Association of IL-10-1082 and IL-10-592 polymorphisms with chronic hepatitis B and/or hepatitis C virus infection among plasma donors in a rural area of Hebei Province, China. Wei Sheng Yan Jiu, 40(6): 709-713.
12. Zhang L-Z, Zhang T-C, Pan F-M, Zhang Z-H, Li X (2010) Interleukin-10 gene polymorphisms in association with susceptibility to chronic hepatitis C virus infection: a meta-analysis study. Arch Virol., 155: 1839-1842.
13. Vidigal PG, Germer JJ, Zein NN (2002) Polymorphisms in the interleukin-10, tumor necrosis factor-alpha and transforming growth factor-beta1 genes in chronic hepatitis C patients treated with interferon and ribavirin. J. Hepatol., 36: 271-277.
14. Abe H, Aizawa Y, Takahashi H, Amano K, Zeniya M (2003) Single Nucleotide Polymorphisms in the Interleukin10 Gene Promoter and Clinical Outcome of Chronic Hepatitis C Virus Infection. Jikeikai Med. J., 50: 159-166.
15. Bouzgarrou N, Hassen E, Mahfoudh W, Gabbouij S, Schoerer E, Ben Yahia A, Ben Mami N, Triki H, Chouchane L (2009) NS5AISDR-V3 region genetic variability of Tunisian HCV-1b strains: correlation with the response to the combined Interferon/Ribavirin therapy. J. Med. Virol., 81:2021-2028.
16. Persico M, Capasso M, Persico E, Masarone M, Renzo Ad, Spano D, Bruno S, Iolascon A (2006) Interleukin-10 - 1082 GG polymorphism influences the occurrence and the clinical characteristics of hepatitis C virus infection. J. Hepatol., 45(6):779-85.
17. Gao Q, Liu DW, Zhang SY (2009) Polymorphisms of some cytokines and chronic hepatitis B and C virus infection. World J. Gastroenterol., 15(44):5610-5619.
18. Oleksyk TK, Thio CL, Truelove AL, Goedert JJ, Donfield SM, Kirk GD, Thomas DL, O'Brien SJ, Smith MW (2005) Single nucleotide polymorphisms and haplotypes in the IL10 region associated with HCV clearance. Genes Immun., 6: 347-357.
19. Kusumoto K, Uto H, Hayashi K, Takahama Y, Nakao H, Suruki R, Stuver SO, Ido A, Tsubouchi H (2006) Interleukin-10 or tumor necrosis factor-alpha polymorphisms and the natural course of hepatitis C virus infection in a hyperendemic area of Japan. Cytokine, 34: 24-31.
20. Reuss E, Fimmers R, Kruger A, Becker C, Rittner C, Hohler T (2002) Differential regulation of interleukin-10 production by genetic and environmental factors: a twin study. Genes Immun., 3: 407-413.
21. Baghi Sahand, Alavian Seyed, Mehrnoush Leila, Salimi Shima (2015) Impact of the IL-10 Promoter Gene Polymorphisms in the Severity of Chronic Hepatitis B Infection. Hepatitis monthly, 15(7): e28287.
22. Day DE, Kaufmann P, Kiepiela JA, Brown ES, Moodley S, Reddy EW, Mackey JD, Miller AJ Leslie, C Depierres (2006) PD-1 expression on HIV-specific T cells is associated with T-cell exhaustion and disease progression. Nature, 443: 350-354.
23. Zdanov, Alexander (2004) Structural Features of the Interleukin-10 Family of Cytokines. Current pharmaceutical design, 10: 3873-84.
24. Bruno CM, Valenti M, Bertino G, Ardiri A, Amoroso A, Consolo M, Mazzarino CM, Neri S (2011) Relationship between circulating interleukin-10 and histological

©2009-2020, JGPT. All Rights Reserved

features in patients with chronic C hepatitis. Ann Saudi Med. Jul-Aug; 31(4):360-4.

25. Kamanaka M., Kim ST, Wan Y, Sutterwala FS, Lara-Tejero M, Galán JE, Harhaj E, Flavell RA (2006) Expression of interleukin-10 in intestinal lymphocytes detected by an interleukin-10 reporter knockin tiger mouse. Immunity, 25(6):941-52.
26. Couper KN, Blount DG, Riley EM (2008) IL-10: the master regulator of immunity to infection. J. Immunol., 180: 5771-5777.
27. CL Day, DE Kaufmann, P Kiepiela, JA Brown, ES Moodley, S Reddy, EW Mackey, JD Miller, AJ Leslie, C Depierres (2006) PD-1 expression on HIV-specific T cells is associated with T-cell exhaustion and disease progression. Nature, 443: 350-354.

©2009-2020, JGPT. All Rights Reserved