

## Genetic Variations in Host Factors and their Critical Role on HCV Medication

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### Abstract

Although standard treatments are nearly life-saving in hepatitis C patients, all patients equal don't respond to such medications. To achieve an efficient therapeutic response in all patients, medications should individually alter based on genetic factor variations. Hence, having more detailed knowledge of the affective factors on the disease promotion could help us to organize an appropriate regime to treat HCV patients. In order to review recent studies on HCV-related treatments, the data was collected from the clinical and molecular studies published during the last 15 years in electronic databases such as PubMed, Google Scholar, Medline, Scopus and Web of Sciences. Thus, this literature reviews the recent clinical studies with the genetic-based aspects, especially those factors affecting the etiopathological and histological feature of hepatitis C, diagnostic genetic and viral affecting criteria as well as some effective treatment strategies.

**Keywords:** Hepatitis C Virus; Genetic Host Factors; Sustained Virologic Response

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### Introduction

Hepatitis C is one of the rising disastrous problems worldwide. Approximately, 170-200 million people 3-3.5% of the world population suffer from hepatitis C virus (HCV) infection with the risk of morbidity and mortality (1-3). Around 3-4 million persons are infected each year and more than 350,000 people die every year from hepatitis C-related liver diseases (4-6).

Amongst different groups of the patients with acute HCV infection, only 15-30% could spontaneous clear the virus while the other patients have potential for promoting severe progressive liver damage (7, 8). Based on the literature reports, about 70-85% of HCV infected patients develop to the chronic stage, and in 20-30% of them it leads to liver cirrhosis associated with hepatocellular carcinoma (HCC) with 1-5% death rate caused by liver cancer (8,9). Considering that several epidemiological studies were conducted in different societies, up to 80% of HCC cases were reported in East Asia and Sub Saharan Africa while only 13% occurred in America (10).

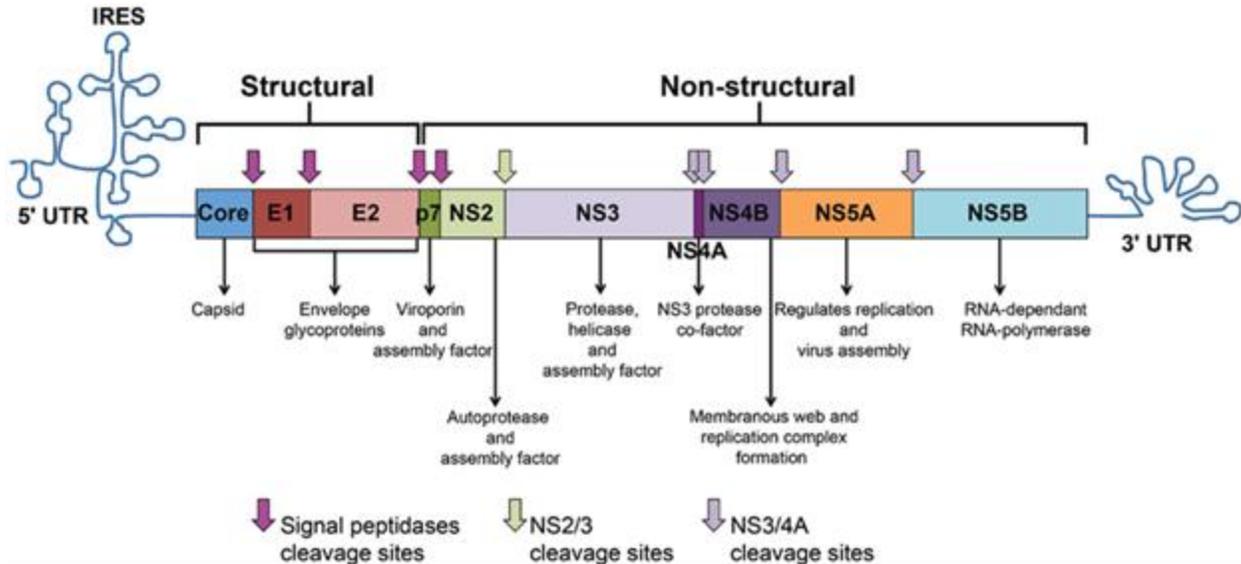
Therefore, from the point of epidemiologic view, HCV infection includes unequal frequencies in different geographic regions; so that, the highest rate of HCV infection occurs in Far East Asian countries (11). Taken together, the prevalence of HCV in some countries of Far East Asia, Africa, South East Asia and East Mediterranean are higher than Europe and North American countries (12, 13, 14).

### *Hepatitis C virus*

HCV is a small, enveloped positive single-stranded ribonucleic (RNA) virus from hepacivirus genus of Flaviviridae family lacking cytopathic effects (15). As illustrated in Figure 1, whole genome of HCV is 9.6 kb which is flanked by conserved non-translated regions (NTRs). These NTR sequences are required for both RNA translation and replication of HCV genes. An internal ribosome site (IRS) is located near the 5'- NTR, conducting the expression of a polyprotein precursor. Core E1 and E2 are structural proteins, originated from precursor polyprotein

cleavage by alternative translation mechanism. Non-structural genes express several proteins, which included P7, NS2, NS3, NS4, NS4B, NS5A and NS5B. Proliferation of the HCV genome occurs when the genome converted to a double-strand RNA and then negative-strand RNA is used as a replicative template (16, 17). Replication process of HCV genome is driven by an RNA-dependent RNA

polymerase, which product of this reaction is a double-stranded RNA. Subsequently, ATP-dependent NS3 helicase converts the double-stranded RNA into positive single-stranded RNA (18, 19). Despite many current advances in HCV proliferation, there is yet no exact mechanism of infection progression (20).



**Figure 1.** Hepatitis C virus: Model structure and genome organization (21).

The main ways of HCV infection include: 1) Blood transfusion from infected persons, 2) Organ transplant from infected persons; 3) Needlestick cases in hospitals or in health care units; 4) Injection drug users who used sharing syringe; 5) Being born to a hepatitis C-infected mother; 6) Through sex with infected persons; 7) Sharing personal items which were contaminated with infectious blood (4, 22). The HCV infection usually has a different latency period which might take 2 weeks to 6 months; however, about 80% of persons present no symptoms in initial stages of infection (23). On the other hand, some early symptoms including fever, jaundice, abdominal pain, especially pain under the right rib, grey-colored faces, dark urine, vomiting, nausea, fatigue and decreased appetite are the most common indicators for acute infection. However, most patients exhibit no symptoms, which caused a serious difficulty in diagnosing HCV infection (24). The current major approach to detection of HCV infection is the application of anti-HCV, which followed by the RIBA and viral RNA tests. Although many studies performed to design efficient vaccines against HCV, up to now, no one has been able to succeed in such way; hence, it is only treated with antiviral medicines (7).

The most vulnerable people to catch the blood-borne diseases are IV drug users, who are often infected to ADIS and hepatitis, because of collective use of injection equipment and drug solution (25). HCV transmission in 90% of patients were has occurred owing to the use of sharing syringe. Drugs administration and also alcohol abuse are two important co-factors, led to the promotion of disease stage and ultimately, increase mortality and morbidity of HCV patients. Additionally, in most of these patients, at least one co-infection is observed with HIV, EBV and HBV (3). This review focused on viral and host genetic factors possibly affecting the response to treatment, difficulties in HCV clearance and persistence status in patients with hepatitis C.

#### *Viral factors*

Treatment of hepatitis C is influenced by the viral factors including viral genotype, quasi-species, baseline viral load and viral kinetics (i.e., rapid and/or early virological response) which can be used as predictors of response (5, 26). Based on molecular analyses, genotype of HCV has been highly diversified by a large number of mutations, which caused wide variety of single nucleotide

polymorphisms (SNPs) in the HCV genome. As such, various genotypes of HCV show 30-35% nucleotide diversity, and at least seven distinct genetic varieties have been identified based on phylogenetic and sequence analyses of complete viral genomes that are

distributed in different geographical regions (27). Therefore, several genotypes of HCV have been identified several in communities worldwide. Considering the extracted data from literature, 6 different genotypes are introduced in Table 1.

**Table 1.** HCV prevalence in different countries and geographic areas based on genotypic diversities.

Genotype no.	Prevalence location	References
1a	North America and Western Europe	27, 28
1b	United States, Europe and Japan	3
2	developed countries such as	3, 18
3	Thailand and Southeast Asia	18
4	North and Central Africa as well as Middle East countries	27, 28
5	Zimbabwe and other South African countries	18, 27, 28
6	South East Asia such as Hong Kong, Thailand, Indonesia, China, Vietnam, Myanmar and Korea	3, 11, 27, 28, 29

Some mutations in HCV replication emerges from multiple quasi-species of HCV. These emerging genotypes of HCV enable to evade host immune response as well as antiviral drugs through resistance pathways that have been activated by new mutations (18). Therefore, for treating HCV patients, it is a need to identify the type of virus regarding genotypic varieties and single nucleotide polymorphism located in virulence genes of the HCV. The literature has reported that the highest SVR rate is for the patients infected by HCV genotype 2 and the lowest rate in genotypes 1 and 4 (16). Shortening the treatment period and lowering ribavirin dose reduced SVR rate for patients with HCV genotype 1, but not for genotypes 2 and 3. For this reason, some clinical trial studies specifically focused on genotypes 2 and 3 (29, 30).

Additionally, genotype 2 and 6 are more responsive than genotype 1a while, genotype 1b has the highest resistance compared to genotype 2, 6 and 1a (31-33). Although, genotypes 5 and 6 have high similarity to genotypes 3 and 2 respectively, SVR for each genotype differs. Taken together, SVR rate of 40-50% is achieved by following PEG-IFN/RBV therapy in patients with genotype 1, nearly 60% in patients with genotype 4 and 80% in patients with genotype 2 or 3 (5, 13, 34).

#### *Host factors*

Applying an efficient treatment against HCV requires a versatile knowledge about host factors as one of the major issues in achieving a higher SVR. The crucial factors affecting HCV-related infections included age, race, gender, obesity, steatosis, disease severity, alcohol intake, host immune status and genetic

factors (26). Numerous researchers have conducted many experiments on the function of host immune system to determine therapy-induced responses when healthy people are infected with HCV (5, 35). These studies have indicated that immune response and antiviral therapy of HCV infection are strongly altered by multiple host genetics factors. Two important factors including cytokines and chemokines are the main players in the promotion of hepatitis C. These factors have been documented to have key roles in the regulation of innate and adaptive immune response to HCV infection (36-38). Multiple studies have found cytokines gene polymorphisms influence on the pathogenesis of HCV and outcome of response (39, 40). In the literature review, the key roles of the most important host factors associated with HCV infection along with all related genes will be discussed.

#### *1. IL-4*

One of the major cytokines involved in HCV infection is IL-4, secreted by TH2. Therefore, TH2 is responsible for progression or persistence of HCV infection. High-elevated level of IL-4 suppresses inflammatory cytokines leading to lower liver injury. Besides, this occurrence is associated with inability of host to eliminate the virus and progression of a chronic disease (41). The critical role of genetic varieties in the IL-4 gene has recently been reported. In this relation, the allele C (+33) of the IL-4 gene is observed in acute more than the chronic hepatitis. This polymorphism indicated as IL-4 C/T (+33) found to be associated with HCV spontaneous clearance. The IL-4 (+33) T SNP expresses a high level of IL-4 which increases HCV survival rate and

serious liver damage (8).

## 2. *IL-8*

IL-8 is a cytokine stimulated by Th17 lymphocyte from contact with HCV NS5A protein for inhibiting the antiviral activity of INF during the progressive stage (42, 43). Besides, production of HCV-induced IL-8 often resulted in induction of COX-2 expression, followed by liver cell injury-related inflammation (44).

## 3. *IL-10*

IL-10 is classified in class-2 cytokines, which is expressed by TH2. This cytokine is known as an anti-inflammatory factor. Additionally, IL-10 acts via down-regulation of the cytokine gene expression in TH1 and co-stimulatory factors on macrophages. The presence of SNPs located in IL-10 promoter, which alters the IL-10 gene expression can affect several pathways in the immune cells. IL-10 gene expression is strongly associated with SNPs located in regulatory site. One of the most important polymorphisms located in IL-10 gene codon-1082 by which GG genotype results in over-expression of IL-10 protein, causes a low pro-inflammatory response, decreases the liver fibrosis and finally promotes highly spontaneous clearance. This SNP genotype causes down-regulation of IL-10 gene expression and thus weakens antiviral response and contributes HCV infection towards hepatitis chronicity (8).

## 4. *TH17 Modulatory Cytokines*

T helper 17 (TH17) is known as a T cell belonging to a subgroup of TCD4+ which contributes to autoimmune-related inflammatory diseases with production of immune modulators such as IL-17A, IL-17F or IL-22 and IL-16. These cytokines can play a major role in progression of HCC and can increase liver injury in HCC patients (45). Among the cytokines, the most important one, IL-22 mainly secreted by TH17 is a member of IL10 cytokine family and plays pleiotropic protective and pathological roles in different tissues and organs. IL-22 affects hepatocytes and mucosal epithelial cells through specific receptors (46). Two main SNPs in the IL-22 gene including IL-22 rs1012356 A/T and rs1179251 C/G were found to be associated with HCV outcome (47).

## 5. *IL-18*

IL-18 induces interferon- $\gamma$  and thus plays a critical role in activating the T-helper1 (TH1) which efficiently participates in antiviral immune response. The serum IL-18 level was found to be correlated with the severity of liver disease in cirrhotic patients, histological activity score and necrosis (48, 49).

Herein, some single nucleotide polymorphisms (SNPs) of IL18 gene were reported to be associated with spontaneous clearance of HCV infection (50).

## 6. *IL-28B*

A large literature has investigated spontaneous viral clearance and response to treatment associated with IL28B SNPs, located on chromosome 19 which encodes interferon lamda-3 (51-53). The SNPs of Rs809917, rs12979860 and rs12980275 are the main polymorphisms of IL28B gene, which are correlated with the prediction of response to therapy and spontaneous clearance (34, 54). These SNPs are often located in regulatory, transcription initiation or promoter region, which could impress on expression level of L28B cytokine and thereby decrease antiviral defense and spontaneous clearance of HCV infections. In genetic evolution, IL-28B gene includes different genotypes (SNPs) which are in favor of SVR in the HCV patients. Rs12979860 C/C genotype is associated with SVR in Caucasian, Asian, European, Hispanic and African-American populations. The genotype of rs8099917 has been reported to be the strongest predictor marker in genotype 2 and 3 (34, 48). Although rs8099917 GG/GG genotype indicated no SRV rate, the other polymorphism of the rs8099917 SNP like TG/GG allele had high SVR rate and spontaneous clearance in HCV patients in Asian population (5, 55-58). Another favorable IL28B polymorphism, commonly found in Asian population is CC genotype of rs12079860. The patients with CC polymorphism of rs12079860 SNP show spontaneous clearance and SVR rate 2-fold increase in comparison with the patients with TT genotype (56, 59). Additionally, those patients carrying rs12979860 SNP were associated with interferon-free treatment (33, 60, 61).

## 7. *Toll-like receptors (TLRs) genes*

Toll-like receptors (TLRs) are a type of proteins involved in innate immune system. TLRs are derived from the conserved structures with microbial origin. Some of the polymorphisms in TLR genes are found to be associated with viral infection. The TLR2, 4, 7, 8 and TLR9 are the most important elements related to antiviral responses. Several polymorphisms related to the genes of TLR4; rs498690A/G, rs4986791C/T, TLR7; rs179009A/G and TLR8; rs3764879 C/G play critical role on the susceptibility to HCV infection. Additionally, these TLRs can exert their impact on fibrosis progression and graft survival (55, 61-63).

## 8. *Suppressor of cytokine signaling 3 (SOCS3)*

SOCS3 is an inhibitor of IFN- $\alpha$  induced Janus kinase signal transducer and an activator of transcription pathways. SOCS3 polymorphisms influence on the

outcome of antiviral treatment. One polymorphism in -4874 site of SOCS3 gene with the ID name of rs4969170 A/G is the most important SNPs related to HCV therapy. Baseline of SOCS3 expression represents a novel blood biomarker which has the potential to predict the treatment response (26, 64).

#### 9. *PKR protein kinase*

PKR or double-stranded RNA-dependent protein kinase is an interferon stimulating protein in the antiviral state. Some polymorphisms in PKR gene might affect on the treatment of HCV patients, who are under the interferon (INF) therapy. It was found that a polymorphism at position -168C/T in the promoter region of the PKR gene might be associated with natural outcome and also with response to IFN therapy in HCV infection. Additionally, tandem trinucleotide repeats in the promoter region of PKR can influence on the outcome of therapy. Consequently, up to nine of these repeats in PKR promoter were assigned to higher SVR (26, 65).

#### 10. *IL-1 $\beta$*

IL-1 $\beta$  is an initiating factor of inflammation cascade, which inhibits IFN- $\alpha/\beta$  and antiviral activity. When IL-1 $\beta$  increases in the serum of HCV patients, consequently, the response to IFN-based therapy significantly decreases (66). Several SNPs have been reported to be in IL-1 $\beta$  located at positions -31 (rs1143627), -511 (rs16944) and +3953 (rs1143634) which have high importance in HCV infection progression. Patients with genotype 4 with CC genotype have higher rate of SVR than those carrying CT and TT genotypes (26).

#### 11. *Myxovirus resistance A (MxA) gene*

MxA gene is known as interferon stimulating gene, which encodes induced cytoplasmic interferon located in the human cells (67, 68). MxA protein inhibits the replication of many viruses which have negative-sense single-stranded RNA or which are double-stranded RNA viruses. Additionally, MxA might inhibit hepatitis B virus through suppressing viral reverse transcribing DNA (69). SNPs of MxA gene as important genetic host factors can influence on the outcome response to IFN- $\alpha$  in chronic HCV patients (70). Besides, antiviral drugs like ribavirin increases MxA gene expression in the patients (71). Additionally, some of intracellular antiviral proteins such as 2-5 oligoadenylate synthetase, dsRNA-activated protein kinase and MxA are induced by IFN and therefore have a defensive role against HCV infection. MxA protein expression as a sensitive marker for HCV replication could be a favorable predictor factor of SVR in the HCV patients with G4 treated with IFN- $\alpha$ 2 and ribavirin (13). An important

SNP, Rs2071430 located at position -88 MxA gene's promoter region with GG genotype is responsible for lowering MxA expression, whereas TT genotype of the same SNP is associated with protection against HCV infection (72). On the other hand, SNPs which are located on -88 (G/T) and -123 (C/A) of MxA gene promoter are associated with susceptibility to HCV infection and response to IFN- $\alpha$  as well as the natural outcome of hepatitis (68). Based on much literature, ribavirin induces an alternative MxA product with different functions, which acts as an immune-modulator in the pathway related to IFN- $\alpha$  antiviral activity (65, 71).

#### 12. *2'-5'-oligoadenylate synthetase (2'-5'-OAS)*

Oligoadenylate synthetase (2'-5'-OAS) stimulates IFN gene which plays a key role in viral RNA degradation and also inhibits viral replication. A polymorphism of 2'-5'-OAS gene with GG genotypes in 3' UTR region are known as non-responders to viral infection (73). However, several polymorphisms in 2'-5'-OAS gene are associated with susceptibility to HCV infection. A polymorphism of OAS1 gene, including rs2660 SNP located in the 3-untranslated region is found to be associated with the outcome of HCV infection (64).

#### 13. *IL-10*

There are several polymorphisms in the IL-10 promoter, the most important of which include three SNPs; -1082G, -819 and -592. These SNPs have a major role on expression level of IL-10 gene. Therefore, lowering IL-10 expression drives immune system to Th1 type, which results in high-sustained viral clearance (66, 71). Most patients with low expression of IL10 are at high risk of rejection in liver transplantation whereas a polymorphism named RA-rs9610 A/G which lowers IL-10 expression shows a significant relation to HCV outcome (74).

#### 14. *TGF- $\beta$ 1*

Plasma level of TGF- $\beta$ 1 is associated with liver fibrosis progression in HCV patients. TGF- $\beta$ 1 polymorphisms at codon 10 (869) T/C and codon 25 (915) C/G of exon 1 can affect the chronicity of HCV disease and fibrotic progression (75-77). On the other hand, TGF- $\beta$ 1 codon 25 SNP is strongly associated with SVR (76). Additionally, TGF- $\beta$ 1 producing T cells have the ability to predict the absence of spontaneous clearance in patients with acute HCV infection (78).

#### 15. *Particular HLA*

HLA alleles as host genetic factors show an efficient impact on susceptibility as well as the outcome of HCV treatment. For instance, frequencies of

DRB1\*0401, DQB1\*0301 and DQA1\*0501 alleles in the patients infected chronically by HCV showed a significant association with the normal alanine aminotransferase (ALT) group leading the development of the chronic hepatitis C to liver damage and cirrhosis (79).

On the other hand, some of HLA alleles such as HLAB44, HLADR7, DRB1\*0404, DRB1\*0701, DRB1\*11 and DQA1\*0201-DQB1\*02, DQA1\*0501, DQB1\*0301, DRB1\*0401 alleles, DQA1\*0301-DQB1\*0301, DQA1\*0501-DQB1\*0301 and DRB1\*1101-DQB1\*0301 are significantly associated with raising SVR and lowering HCV infection; whereas DQB1\*0201 allele is completely correlated with liver damage promotion in chronic HCV infection (77, 79).

#### 16. Vitamin D receptors

One of the systemic hormones acts as multifunctional factors involved in immune response to microbial infections is vitamin D. This vitamin as an active form, including 1, 25-dihydroxy vitamin D, plays a critical role in immune regulation, cellular growth, programmed cell death and differentiation (80). The level of vitamin D in the body is considered as a predictor of response outcome related to treatment efficiency. High serum concentration of vitamin D is associated with non-SVR in HCV patients NR111 CCA haplotype. In addition, genetic variations in its receptor is associated with susceptibility to viral infection (79). Rs7975232CC SNP located on ApaI gene from VDR gene family contributes to non-SVR. Rs10877012 CC polymorphism in CYP27B1-1260 promoter is responsible for down-regulation of  $\alpha$ -1-hydroxilation process and 25-OH vitamin D formation. This SNP reduces 1, 25 hydroxy vitamin D level and thus the reduced level of 1, 25 hydroxy vitamin D is associated with the failure of SVR in HCV patients with genotypes 1, 2 and 3. Besides, high level of vitamin D causes higher SVR rate which is associated with AA>CA polymorphism in CYP27B1-1260 pomoter gene (12).

#### 17. Inosine Triphosphatase (ITPA)

Studies based on genome-wide analysis showed a significant association between ribavirin, hemolytic anemia and ITPA gene polymorphisms (57). Two important SNPs including Rs1127354 and rs7270101 in ITPA gene are considered as predictors of RBV-induced anemia. Several studies have reported that ITPA deficiency could reduce the rate of ribavirin-induced hemolytic anemia. For the HCV treatment, if taribavirin, which is a ribavirin analog with similar SVR, substituted ribavirin the rate of anemia would significantly decrease (9, 55, 57).

#### 18. Intracellular adhesion molecules (ICAM)

ICAMs are known as cell surface proteins, which are expressed on hepatocytes. These membrane proteins are responsible for inflammation and hepatic damage in chronic HCV. Additionally, sICAM is secreted ICAM that is synthesized by various cell types. When more sICAM is released, there is increased the level of serum alanine aminotransferase that can progress the disease toward HCC in HCV patients. Increasing ICAM-1 expression promotes HCV infection and liver inflammation. Another polymorphism with identifier of Rs281437 located in ICAM-1 gene is strongly associated with progression of hepatic fibrosis in HCV genotype 4 (81).

#### 19. Tumor necrosis factor- $\alpha$ (TNF- $\alpha$ )

TNF- $\alpha$  is type I cytokine which is secreted by monocytes and Kupffer cells. TNF- $\alpha$  is reported to be associated with fibrogenesis via binding to TNF-receptors. Polymorphisms in the TNF- $\alpha$  promoter seem to be related to histological severity at chronic HCV patients. TNF2 (-238A) and TNF3 (-308A) have polymorphisms in their promoter regions which are the cause of increased liver cirrhosis (82). Two other SNPs located in -1031C and -863A of promoter region of TNF- $\alpha$  are significantly associated with increasing the frequency of failure acute hepatitis (83).

#### 20. DC-SIGNR binds to hepatitis C virus

The surface interaction between HCV and DC-SIGNR plays an important role in the pathogenesis of HCV infection. Tandem repeat polymorphisms located within DC-SIGNR gene have been recently reported to be associated with HCV replication. Decreased attachment of DC-SIGNR to HCV might be associated with lower HCV replication. Therefore, the patients carrying less number of tandem repeats, approximately lower than four repeats, have been observed to be less compatible host for HCV replication than those carrying up to nine repeats (84).

#### 21. Apolipoprotein E (APOE)

APOE as a component of VLDL binds to receptors, which HCV used for entering into the cells. There are three isoforms of APOE including: APOE2, APOE3 and APOE4. APOE2 allele typically binds to lipoviral particle and acts as a barrier to the entry of the HCV to cells (85, 86).

#### 22. Osteopontin (OPN) Gene

Osteopontin Gene expresses a secretory protein, which strongly attaches to osteoclasts through hydroxylapatite in the bone matrix. The presence of polymorphisms in OPN gene affect IFN-based therapies in HCV chronic patients. The SNP at the

nucleotide -443 C/T versus C/C and T/T is a favorable predictor for the response to interferon therapy in chronic HCV patients (87).

### **Discussion**

Interferon type I was used as a first line of treatment for HCV infection in 1986. Afterward, ribavirin was added to therapy regime of HCV patients. Aimed at providing more efficient treatment, pegylated interferon -alfa (PEG-IFN- $\alpha$ ) entered to the practical cure of HCV patients in 2001 and its combination with ribavirin was considered as the standard common medicine (69, 88, 89). The therapy regime with the combination of PEG-IFN and ribavirin showed a significant increase in SVR in comparison with conventional therapy in which IFN- $\alpha$  and/or ribavirin were administered separately (5). Telaprevir and Boceprevir were introduced in 2011, which were prescribed as a triple therapy for HCV patients (90). Two other drugs, Sofosbuvir and Simeprevir, which act as inhibitor of NS5B nucleotide polymerase and NS3/4 protease have been also used for HCV treatment since 2013 (34). Faldaprevir and Daclatasvir as new direct-acting antiviral (DAA) medicine were expected to be available in 2015 (91). In spite of the recent therapeutic success with standard-of-care treatment (SOC), several patients are annually reported that unequally respond to the therapy regime. Based on clinical reports, it is evidenced that a combination regime including Peg-IFN and ribavirin plus telaprevir can increase SVR rate of hepatitis C patients with genotype 1 (92). It is expected that new efficient strategies for the treatment of hepatitis C virus infection, may lead to simplified medications with new pharmaceutical drugs. Up to now, scientists are hopeful to develop more specific drug regimes for inhibiting HCV infection and to optimize drugs administration based on individual genetic variations in order to decrease medication side effects in the near future (5).

According to the growing trend of new hepatitis medications, administration of interferon-free regime can be predicted. A combination of faldaprevir and deleobuvir with ribavirin as an interferon-free regime results in 59% SVR rate in HCV patients and also reduces the anemia due to the absence of PEG-IFN adverse effects on the white cells and platelets (92).

The treatment of HCV is expensive and associated with adverse consequences for patients and providers will need to know the likelihood of the response to treatment. The factors which determine this likelihood are called pretreatment response and can be classified into host, viral and environmental factors. Multiple genes are affected when an individual is infected by HCV due to various interactions which occurs between viral and host

factor genes. Therefore, the response to HCV infection in different HCV positive individuals strongly depends on varying factors such as age, race, insulin resistance, obesity, co-infection with EBV, HIV and HBV, drugs, steatosis, alcohol consumption, hyperlipidemia, diabetes and iron (7, 34, 85, 93-95). Despite many advances for treating and recovering the HCV infected patients, most health professionals are poorly aware of the new strategies to enhance HCV assessment and treatment [100]. Although, the prediction outcome of response is not exactly satisfying, most laboratories trails need to achieve the appropriate predictors. For instance, occasionally, biomarkers used for detection of early HCC can alter treatment decision and improve patient's survival. In addition, several gene polymorphisms, which are related to immune response and influence the outcome of acute and chronic HCV infection, facilitate the response prediction.

### **Conclusion**

Recently, combination of PEG-IFN- $\alpha$  and ribavirin is considered as the standard and common treatment for HCV. Although some medications have emerged for improving the treatment regime of HCV, none of them shows the same efficiency in all patients. Therefore, it seems that there is no practical medication for preventing HCV infection worldwide. Taken together, HCV treatment has many limitations, which host genetic factors are most important causes of progression of HCV infection. The most efficient strategy for HCV medications is to drive immune response towards cellular immune system which activates TH1 and directs the disease to acute infection. Considering that acute infectious hepatitis shows high SVR and viral clearance, a favorable medication can improve HCV treatment for all patients. Analysis of gene polymorphisms can help to better understanding of interactions of host and virus and may consequently lead to prediction of the sustained virological response to antiviral therapy. Besides, those patients with adverse alleles may benefit from additional treatment strategies.

### **Author Contributions**

All authors have the same contribution in preparation of data and manuscript writing.

### **Conflict of Interest**

There is no conflict of interest in this review article.

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