Hepatitis C: Viral Features and Clinical Aspects

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Abstract

Knowledge on hepatitis caused by hepatitis C virus (HCV) has increased since 1989, when the virus was identified and cloned from the complementary deoxyribonucleic acid (DNA) extracted from cells of an experimentally infected chimpanzee with the virus of hepatitis non-A, non-B. Approximately 90% of cases of post-transfusion hepatitis and 50% to 70% of sporadic cases of hepatitis non-A and non-B were caused by HCV. Thus, the discovery of this virus has enabled the development of serological diagnosis techniques. In recent years, there have been major advances in the characterization of the molecular structure of HCV, the development of diagnostic tests with high specificity and sensitivity, knowledge about the pathogenic mechanisms and improved therapeutic options. The continued study of this disease allowed the characterization of its epidemiology and main routes of transmission. Currently, HCV competes with alcoholic liver disease as the leading cause of chronic liver disease. As shown asymptomatic in most cases, this disease progresses silently for chronicity with a consequent increase in cases of liver cirrhosis and hepatocellular carcinoma (HCC). This study reviews the main aspects of the hepatitis C. HCV infection is progressive, silent and causes the patient serious complications such as cirrhosis and HCC, and brings high costs to the government. Therefore, given the diversity of problems caused by epidemic HCV, this study is essential to new discoveries about this health problem.

Keywords: Hepatitis C; Liver disease; Epidemiology; Cytokines

Introduction

Infection with hepatitis C is a current and important global public health problem, being the leading cause of chronic liver disease and the most common indication for liver transplantation in developed countries. According to the World Health Organization (WHO), about 3% of the general population is infected with HCV. A small fraction of the population reaches viral clearance spontaneously, whereas around 85% of infected individuals progress to chronic infection, which constitutes a risk factor for the development of cirrhosis and HCC and cooperates with the increasing number of liver transplants.

Prati points out that HCV infection represented a serious problem for blood banks and receivers in the 1980s, for upto 10% of blood units transmitted the virus. It was only in mid-1993 that screening tests for HCV in blood donors were implemented, reducing drastically the transmission of the virus through blood transfusion, which has become more secure. However, there are still some individuals who contracted HCV before 1993 through transfusion of blood and/or blood products [1,2].

At present, the main goal of hepatitis C treatment is to control the progression of liver disease by inhibiting viral replication and achieving sustained virological response (SVR), determined as viral particles undetectable in plasma six months after the end of treatment. The therapeutic schemes available by the Ministry of Health are dual therapy, involving the conventional interferon (IFN) or pegylated interferon plus ribavirin (RBV), and triple therapy, which adds to the dual therapy a protease inhibitor (PI), boceprevir or telaprevir. Recently, the National Health Surveillance Agency (ANVISA) has approved Daclatasvir as a pan-genotypic inhibitor of the nonstructural protein 5A (NS5A), which will soon be included in the protocol.

Cytokines have a fundamental role in regulating the immune response. In infections caused by hepatitis C virus, cytokine production levels appear to interfere with disease progression, viral persistence and therapeutic response. Cytokine genes are polymorphic in specific sites and specific polymorphisms located in coding/regulatory regions alter the expression and secretion of cytokines.

The single nucleotide polymorphism in interleukin 10 gene (IL10) seems to be associated with the success of treatment, i.e. when the patient reaches SVR. According to the proposed therapeutically schemes, SVR rates can reach 50% to 90% of treated people, thereby reducing the development of cirrhosis and liver cancer. However, the access to the diagnosis and treatment remains very low [2].

Thus, this paper reviews the main aspects of the C virus in an attempt to understand this disease better.

Hepatitis C Virus

HCV is a virus of the Flaviviridae family, genus Hepacivirus, with linear single-stranded ribonucleic acid (RNA) genome, positive polarity and approximately 9.5 kilobases (kb). It is an enveloped virus with a diameter ranging from 55 to 65 nanometers (nm) with icosahedral symmetry. The lipidic

envelope originates from the membrane and the core composes the capsid. The proteins envelope 1 (E1) and envelope 2 (E2) stand out in the envelope, which form very important tetramers recognizing receptors of the host cell [3,4].

The HCV genome has about 9,500 nucleotides arranged in a single long open reading frame (ORF) that comprises the entire genome and encodes a single polyprotein of about 3,000 amino acids. As many other viruses with similar genomic constitution virus, the RNA molecule acts as messenger RNA (mRNA) to translate viral proteins [4]. The viral polyprotein newly translated is cleaved by a protease combination of the host cell and viral proteases to form the viral structural (Core, E1 and E2) and non-structural (NS) proteins (NS2; NS3; NS4A; NS4B; NS5A; and NS5B) [5,6].

Viral tropism, receptors and replicative cycle

The union of the virus to hepatocytes proteins triggers the process of endocytosis, allowing the internalization of viral particles in the host cell and release of viral RNA in the cytoplasm [7,8].

The HCV replication cycle begins with its binding on the host cell membrane, triggering the interaction of viral glycoproteins and glycosaminoglycan's (GAG) present on the cell surface [9]. This process takes place simultaneously to the interaction of low density lipoproteins (LDL) with low density lipoprotein receptors (LDL-R) present in the membranes of hepatocytes, as it is assumed that LDL associates with viral particles [10]. Subsequently, the scavenger receptor class B type I (SR-BI) interacts with the tetraspanin CD81, which binds to the viral envelope proteins [11,12].

Whether SR-B1 interacts with the CD81, the association with the viral envelope proteins is facilitated. CD81, together with a tight junction (TJ) protein called claudin 1 (CLDN1), naturally form a complex essential for HCV entry. After the complex CD81/CLDN1 linkage, HCV interacts with the occludin (OCLN), another tight junction protein, allowing the viral internalization [13]. Other molecules, such as the transferrin receptor (TfR) and the tetraspanin CD63, appear to be involved in the HCV entry, though their mechanisms are not well understood. The internalization through endocytosis is probably favored by the lipid properties of SR-BI. After merging with the membrane and the low potential of hydrogen (pH) of the cytosol, the viral genome is released for translation and processing of the polyprotein. It is worth highlighting that studies demonstrated activated macrophages producing tumor necrosis factor alpha (TNF-α), increasing the diffusion coefficient of CD81 and relocating the OCLN in the basolateral membrane, therefore facilitating the entry of HCV [14].

The CD81 is a protein of the tetraspanin family, consisting of four transmembrane sequences, a small extracellular loop and a large extracellular loop, which is the portion that interacts with the E2 protein [15]. CD81 is expressed in the majority of mammalian cells with different functions: cell adhesion, mobility, activation and signal transduction [16].

The SR-B1, highly expressed in the liver, is a multiple binding agent functioning as a receptor for several classes of lipoproteins. Therefore, it has been proposed as a cellular receptor due to its affinity with viral E2 protein fraction [17].

However, other molecules that also express CD81 and SR-B1 receptors are not susceptible to HCV infection, suggesting that hepatic surface molecules are required for the entry of the virus into the host cell [17].

The IRES promotes viral fitting with the ribosome to initiate the translation of the coding region that will synthesize viral polyproteins, which are processed to generate mature proteins. NS5B protein has RNA polymerase activity, becoming the central part of the replication machinery that uses the viral genome as a template for transcription of a negative sense complementary RNA molecule. This negative sense is a template for the synthesis of new RNA molecules of positive polarity that form the genome of new viral particles [18,19].

HCV genotypes

HCV is enormously heterogeneous in the sequence of nucleotides in different regions of the viral genome. Phylogenetic analysis of genomic sequences allowed the characterization of seven main genotypes which are subdivided into subtypes a, b and c, among others [20-22]. The genotyping is essential as it presents different predictive values in the response to antiviral therapy, with the best response associated with genotypes 2 and 3 compared to genotype 1 [23].

Within the same genotype and subtype, variations termed quasi species can be observed. This is possible due to the imperfect replication of the virus, leading to small and constant mutations. The quasi species are about 1% or 2% different in their genomic composition and may be present in early infection or arise during the infection as a mechanism of escape and adaptation to the body's defences. This variation capability facilitates the development from acute to chronic infection, explains antiviral therapy resistance and hinders the development of vaccines [24,25].

The clinical implications of high viral heterogeneity are related to the adaptation, avoidance and control of the host immune system response and differential sensitivity to antiviral therapy by the virus [23,26].

Treatment of Hepatitis C

According to the proposed therapeutic schemes, the success rate can reach 50% to 90% of people treated, thereby reducing the development of cirrhosis and liver cancer. However, the access to diagnosis and treatment remains very low [2].

The main goal of the treatment is to stop the progression of liver disease by inhibiting viral replication. The treatment is only considered successful when the patient reaches SVR and the virus is eradicated from the blood and liver tissue, despite remaining latent in some cells of the organism [22,24,27].

The main adversities in the treatment of hepatitis C are the clinical and laboratory manifestations. Many side effects are caused by the administration of IFN and RBV. Changes such as pancytopenia, severe anaemia and digestive bleeding are

common in these patients. In these situations, it is appropriate to discontinue the treatment until the patient improves [28].

Thus, early detection has been considered an important factor in clinical practice for the treatment of HCV. The earlier the detection of viral infection, symptomatic or not, the greater the association with SVR. On the other hand, the later the detection, the smaller the association with SVR [29,30].

The spontaneous viral clearance occurs more frequently during the first 12 weeks after the infection initiates. In acute hepatitis C, particularly in icteric patients, spontaneous viral clearance may occur in 15% to 45% of the symptomatic cases. In infections caused by genotype 3, the probability of spontaneous viral clearance is greater [31].

Although genotypes 2 and 3 are historically grouped in the same consensus of treatment, clinical symptoms such as fatty liver, rapid progression to fibrosis and an increased risk for HCC are different, for genotype 3 presents greater incidence of such symptoms [22,27,32].

Transmission

The main factor associated with HCV transmission is the exposure to blood and blood products through transfusions [23]. Studies show that HCV was the causal agent of more than 80% of post-transfusion hepatitis in the 1990s, thus highlighting the requirement of serological tests in candidates to blood donors from 1993 onwards, when the Health Ministry imposed their implementation in blood banks [24]. The high percutaneous exposure in medical and dental procedures, acupuncture, tattoos and manicures, transfusion of blood and blood products from untested donors for anti-HCV, organ transplants from infected donors, intravenous drug use (IDU), hemodialysis and occupational exposure to blood or blood products have been listed as means of transmission [33].

Therefore, any possibly infected material such as cuticle cutters, razor blades and syringes become possible transmitters when shared. In the reported sporadic cases, after blood transfusion and IDU were excluded, there was a significant increase in patients contaminated in surgery and/or hospital care, corroborating the hypothesis already confirmed of transmission during surgical procedures. After the occupational exposure, there is no measure to reduce the risk of infection. The only way to reduce risk is to prevent the accident itself. However, the vertical transmission of hepatitis C virus has much lower rates compared to hepatitis B and occurs in approximately 5% of children born from infected mothers who have high VL. However, in patients co-infected with human immunodeficiency virus (HIV), the risk of transmission is about four times higher [34].

Epidemiology

Infection with hepatitis C virus is considered a public health problem with an estimated 3% of worldwide prevalence. Between 5% and 20% of infected patients develop cirrhosis and 1 to 4% of them develop HCC [35]. The high prevalence occurs in countries in Africa and Asia, whereas countries of North America

and northern and western Europe and Australia have low prevalence. In Africa, the prevalence is higher than 2.9%, while in northern Europe varies from 0.1% to 1%. Sweden is the country with the lowest prevalence (0.003%), while Egypt has the highest prevalence, from 18% to 23%, with genotype 4 responsible for 90% of infections [36-38].

In Latin America, it is estimated that the virus C infected 10 million people. The prevalence in blood donors is 0.69% in Paraguay, 0.66% in Mexico, 0.65% in Argentina, 0.57% in Peru, 0.56% in Bolivia and 0.9% in Chile [39]. In Brazil, found prevalence among blood donors from the Federal District of 0.2%. It is estimated that 2.5 to 4.9% of the population carry HCV, meaning 3.9 to 7.6 millions of people at risk of developing cirrhosis or HCC [40].

The distribution of HCV genotypes is uneven around the world. Genotypes 1, 2 and 3 and their subtypes are widely distributed, while others are restricted to certain areas [21,38,41]. Genotype 4 is prevalent in North Africa, the Middle East and Europe, whereas genotypes 5 and 6 prevail in South Africa and in Southeast Asia [42]. Genotype 7 was registered in Canada in an immigrant from Central Africa. In Brazil, genotype 1 (65%) and 3 (30%) are the most prevalent, followed by 2 (5%) [38,43]. In a recent study with blood donors from Thailand, the prevalence and distribution of genotypes was 71.7% of genotype 3a, followed by 7.5% of genotypes 1a, 7.5% of 1b, 3.8% of 6i, 2.8% of 6f and 1.9% of 6n [44].

In northern Europe and North America, the subtype 1a is the most found and subtype 1b is prevalent in Japan as well as in Southern and Eastern Europe [45]. The subtypes 2a and 2b are also widely distributed, representing 10% to 30% of HCV genotypes [33].

Pathogenesis

Chronic infection caused by hepatitis C virus evolves slowly and may have great clinical and laboratory range from asymptomatic with normal liver enzymes to intensely active forms, progressing to cirrhosis and HCC with elevated enzymes [24].

The process of interaction between the hepatitis C virus and the host results in elimination of the virus or establishment of chronic infection. As previously mentioned, HCV has the capacity to evade the immune response due to its high variability, leading to viral persistence, extent and severity of hepatic injury and possibly HCC, even in immunocompetent patients [26].

Chronic HCV infection occurs in 50% to 80% of infected individuals, and the inability of the immune system to eliminate the virus is poorly elucidated. It is known that the host immune system, which responds by activating cellular and humoral mechanisms when interacting with the virus, may be insufficient to eradicate the infection. Spontaneous viral clearance and the development of persistent infection are not well defined, but studies with genetic association revealed the importance of genes related to immunity in the susceptibility and progression of pathogenesis [46].

Once chronic infection is established, the response of CD4^{+} and CD8^{+} specific T cells is quantitatively weak, providing low selection pressure and causing more escape mutations. However, they produce intrahepatic IFN-γ, which has antiviral action and is essential in the action of T-cells [47-49].

The liver parenchyma is rich in NK, which, when activated, are responsible for recruiting HCV-specific T cells and inducing antiviral activity. This mechanism can eliminate infected hepatocytes, thereby limiting viral replication and contributing to liver tissue damage during the immune response. The hepatitis C virus has the ability to infect not only hepatocytes but also immune cells such as B and T lymphocytes [48].

The presence of C virus in lymphocytes and monocytes is widely known, suggesting possible extra hepatic sites of viral replication interfering in the pathogenesis [50]. Pileri et al. affirm that the receptor protein CD81, which interacts with the E2 fraction, is present both in hepatocytes and lymphocytes [12].

According to Kato et al., the pathogenesis of hepatitis C is related to the interaction of viral proteins with the host, since they can initiate cellular processes such as proliferation, differentiation and apoptosis [51].

Liver fibrosis is the result of repetitive injuries caused to hepatocytes due to HCV infection and action of the immune response. In cases of acute hepatic injury, necrotic tissue is removed and replaced by new hepatocytes, which is a process associated with proinflammatory response and limited deposition of extracellular matrix. If the injury persists, the regenerative process fails and an abundant amount of extracellular matrix is deposited, forming the fibrosis. The injuries induce different degrees of fibrosis, which are classified into initial F0, F1 and F2 and advanced F3 and F4 [52]. TGF-β1 plays a key role among the cytokines in the fibrogenesis process, stimulating the synthesis of extracellular matrix and inhibiting fibrolysis, as well as inducing neutrophil infiltration in the liver and promoting apoptosis through a mitochondrial stimulus. TNF-α has also been observed participating in the fibrogenesis process, and its intrahepatic levels are increased in individuals affected by chronic hepatitis C [53].

The hepatocyte becomes injured through the recognition of the immune system of the infected cell and subsequent destruction. This process of cell destruction is highly variable, resulting in necrosis and inflammation of liver cells with different intensities. The unsuccessful attempt of viral elimination causes a continuous and inefficient inflammatory process, one of the main mechanisms responsible for fibrogenesis [54].

Cytokines produced in the liver are closely related to antiviral activity, but also to hepatocellular injury in most patients with chronic infection. Another aggravating factor is the imbalance between the immunostimulatory and inhibitory cytokines in the persistent infection, resulting in fibrosis, necrosis and consequently in chronic liver disease [55,56].

Genetic susceptibility

The interaction complex of the injuring agent with the immune system and environment are decisive factors for the development of infectious disease. The severity and degree of disease progression are genetically linked [57,58]. The immune system's response to infectious diseases is part of a rigorous and complex system genetically controlled and characterized by being polygenic and multifactorial [58,59].

The first immunogenetic studies associated with hepatitis C have been developed with the human leukocyte antigen (HLA), which demonstrated the association of alleles with viral clearance and susceptibility and progression of infection [60,61]. Consequently, other genes have been investigated, relating new genetic factors to viral infection. However, greater interest is being given to the study of genes related directly or indirectly with the response to the treatment with IFN. Some polymorphisms in the genes for interleukin (IL) 1, IL6, IL10, IL28 and TNF-α and β have been studied in various populations, though they present conflicting results [62-65].

Regarding the host, many factors are involved in determining the severity of the individual disease progression and therapeutic response. There is ample evidence that genetic factors are also associated with the development of infectious disease [57,58]. Studies report that mechanisms related to innate immunity have genetic variability in encoding genes, demonstrating differences in susceptibility, severity and response to therapy of infectious and autoimmune diseases [66].

From the elucidation of the human genome sequence, there was great progress in relation to the structural organization and functioning of genes involved in the innate immune response. These genes are highly conserved among species, and studies show variability between individuals mainly in the form of single nucleotide polymorphism (SNP) [66,67]. Other genetic alterations such as sequence deletions and microsatellites are also found in these genes in both regulatory and coding regions, according to Hinds et al. and Lazarus et al. [66,67]. The cytokines produced in the liver are essential in the immune response against the virus C, but are also associated with liver cell injury.

During viral infection, changes in the balance of stimulatory and inhibitory cytokines can enhance the inflammatory process, favoring necrosis, fibrosis and HCC. Studies have associated cytokine expression levels with the degree of liver damage and the response to antiviral therapy [68].

The SNP study associated with increased plasma levels of cytokines such as interleukin 6 (IL6), IL10, interleukin 28 (IL28), tumor necrosis factor alpha (TNF-α), transformation and growth factor and beta growth 1 (TGF-β1), among others, has been linked to the SVR and viral clearance in hepatitis C [65,69]. Other factors such as age, sex, degree of liver fibrosis, obesity, hepatic steatosis and insulin resistance are also associated with SVR [64].

Conclusion

Major advances occurred in recent years in the immune knowledge, diagnostic and especially treatment of hepatitis C, providing new therapeutic drugs with excellent results and few side effects. However, the mobilization of health organizations is required to develop strategies for preventing transmissions, evaluating at-risk populations and contributing to the decline of prevalence.

References

1. Prati D (2006) Transmission of hepatitis C virus by blood transfusions and other medical procedures: A global review. J Hepatol 45: 607-616.

2. World Health Organization (2014) Hepatitis C Fact Sheet 164.

3. Blackard JT, Shata MT, Shire NJ, Sherman KE (2008) Acute hepatitis C virus infection: A chronic problem. Hepatology 47: 321-331.

4. Kupfer DJ, Frank E, Phillips ML (2012) Major depressive disorder: New clinical, neurobiological, and treatment perspectives. Lancet 379(9820): 1045-1055.

5. Pawlotsky JM (2004) Pathophysiology of hepatitis C virus infection and related liver disease. Trends Microbiol 12: 96-102.

6. Chindamo MC, Soares JAS, Coelho HSM (2010) Hepatite crônica pelo vírus C. In: Mattos AA, Dantas- Corrêa EB. Tratado de hepatologia. Rio de Janeiro: Rúbio: 211-217.

7. Smith AE, Helenius A (2004) How viruses enter animals cells. Science 304: 237-242.

8. Rice CM, Lindenbach BD (2005) Unravelling hepatitis C virus replication from genome to function. Nature 436: 933-938.

9. Germi R, Crance JM, Garin D (2002) Cellular glycosaminoglycans and low density lipoprotein receptor are involved in hepatitis C virus adsorption. J Med Virol 68: 206-215.

10. Dubuisson J, Helle F, Cocquerel L (2008) Early steps of the hepatitis C virus life cycle. Cell Microbiol 10: 821-827.

11. Scarselli E, Ansuini H, Cerino R (2002) The human scavenger receptor class B type I is a novel candidate receptor for the hepatitis C virus. Embo J 21: 5017-5025.

12. Pileri P, Uematsu Y, Campagnoli S (1998) Binding of hepatitis C virus to CD81. Science 282: 938-941.

13. Evans MJ, Von Hahn T, Tscherne DM (2007) Claudin-1 is a hepatitis C virus co-receptor required for a late step in entry. Nature 446: 801-805.

14. Feneant L, Levy S, Cocquered L (2014) CD81 and hepatites C vírus (HCV) infection. Viruses: 535-572.

15. Flint M, Hahn TV, Zhang J (2006) Diverse CD81 proteins support hepatitis C virus infection. J Virol 80:1331-11342.

16. Levy S, Todd SC, Maecker HT (1998) CD81 (TAPA-1): a molecule involved in signal transduction and cell adhesion in the immune system. Annu Rev Immunol 16: 89-109.

17. Martin P, Fabrizi F (2005) Treatment of chronic hepatitis C in patients with renal failure. Clin Gastroenterol Hepatol 3: S113-S117.

18. Lopez RA (2003) Centro regional de investigaciones biomédicas. Faculdade de Medicina UCLM: 30-42.

19. Bartenschlager R, Lohmann V (2000) Replication of hepatitis C vírus. J Gen Virol 81: 1631-1648.

20. Bowen DG, Walker CM (2005) Adaptive immune responses in acute and chronic hepatitis C virus infection. Nature 436: 946-952.

21. Simmonds P, Bukh J, Combet C (2005) Consensus proposals for a unified system of nomenclature of hepatitis C virus genotypes. Hepatology : 962-973.

22. Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB (2011) An update on treatment of genotype 1 chronic hepatitis C virus infection: Practice guideline by the American Association for the Study of Liver Diseases. Hepatology 54: 1433-1444.

23. Lauer GM, Walker BD (2001) Medical progress: Hepatitis C virus infection. N Engl J Med 345: 41-52.

24. Strauss E (2001) Hepatite C. Revista da Sociedade Brasileira de Medicina tropical 34: 69-82.

25. Augusto F, Lobato C (2001) Hepatite C aguda. Reunião anual da NGHD, novembro de.

26. Galé MJR, Foy EM (2005) Evasion of intracellular host defence by hepatitis C virus. Nature 436: 939-945.

27. European Association for the Study of the Liver (EASL) (2011) Clinical practice guidelines: Management of hepatitis C virus infection. J Hepatol 55: 245-264.

28. Rumi M, Aghemo A, Prati GM (2009) Randomized study of peginterferon-± 2a plus ribavirin versus peginterferon-± 2b plus ribavirin in chronic hepatitis C. Gastroenterology 138: 108-115.

29. Corey KE, Mendez-Navarro J, Gorospe EC (2010) Early treatment improves outcomes in acute hepatitis C virus infection: A meta-analysis. J Viral Hepat 17: 201-207.

30. Wedemeyer H, Manns MP (2002) Acute hepatitis C-therapy with interferon α2b. Internest [S.l.]: 1477-1478 .

31. Hofer H, Watkins-Riedel T, Janata O (2003) Spontaneous viral clearance in patients with acute hepatitis C can be redicted by repeated measurements of serum viral load. Hepatology 37: 60-64.

32. Tapper EB, Afdhal NH (2013) Is 3 the new 1: Perspectives on virology, natural history and treatment for hepatitis C genotype 3. J Viral Hepat 20: 669-677.

33. Alter MJ (2007) Epidemiology of hepatitis C virus infection. World J Gastroenterol 13: 2436-2441.

34. Brasil (2011) Boletim Epidemiológico Hepatites Virais . Departamento De AIDS, DEHV, Secretaria De Vigilância Em Saúde: Ministério da Saúde.

35. Yen T, Keeffe EB, Ahmed A (2003) The epidemiology of hepatitis C virus infection. J Clin Gastroenterol 36: 47-53

36. Shepard CW, Finelli L, Alter MJ (2005) Global epidemiology of hepatitis C virus infection. Lancet Infect. Dis 5: 558-567.

37. Baldo V, Baldovi N, Trivello R, Floreani A (2008) Epidemiology of hepatitis C. Curr Pharm Des: 1646-1654.

38. Bruggmann P, Berg T, Ovrehus ALH (2014) Historical epidemiology of hepatitis C virus (HCV) in selected countries. J Viral Hepat 21: 5-33.

39. Dehesa-Violante M, Nunez-Nateras R (2007) Epidemiology of hepatitis virus B and C. Arch Med Res 38: 606-611.

40. Siciliano RF, Boulos M (2004) A revision of hepatitis C treatment. Arq Gastroenterol 41: 1-2.

41. Laperche S, Le Marrec N, Girault A (2005) Simultaneous detection of hepatitis C virus (HCV) core antigen and anti-HCV antibodies improves the early detection of HCV. J Clin Microbiol 43: 3877-3883.

42. Zein NN (2000) Clinical significance of hepatitis C virus genotypes. Clin Microbiol Rev 13: 223-235.

43. Campiotto S, Pinho JR, Carrilho FJ (2005) Geographic distribution of hepatitis C virus genotypes in Brazil. Braz J Med Biol Res 38: 41-49.

44. Barusrux S, Sengthong C, Urwijitaroon Y (2014) Epidemiology of hepatitis C virus genotypes in northeastern thai blood samples. Asian Pac J Cancer Prev 15: 8837-8842.

45. Farci P, Purcell RH (2000) Clinical significance of hepatitis C virus genotypes and quasispecies. Semin Liver Dis 20: 103-126.

46. Chen S, Wang YM (2007) Evolutionary study of hepatitis C virus envelope genes during primary infection. Chin Med Journal 120: 2174-2180.

47. Chang KM (2003) Immunopathogenesis of hepatitis C virus infection. Clin Liver Dis 7: 89-105.

48. Gigi E, Raptopoulou-Gigi M, Kalogeridis A (2008) Cytokine mRNA expression in hepatitis C virus infection: TH1-TH2 cytokine profile in subjects with self-limited disease. J Viral Hepat 15: 145-154.

49. Sun X, Wu J, Shi KQ, Tang KF (2013) Relationship between il-10 gene -1082A/G and -592C/A polymorphisms and the risk of hepatitis C infection. J Viral Hepat 20: 602-611.

50. Sáez-Alquezar A, Bassit L, Sabino EC (2001) Hepatites virais. In: FerreiraWA and Ávila SLM. Diagnóstico laboratorial das principais doenças infecciosas e auto-imunes. Rio de Janeiro: Guanabara Koogan.

51. Kato N, Yoshida H, Ono-Nita SK (2000) Activation of intracellular signaling by Hepatitis B and C viruses: C-viral core is the most potent signal inducer. Hepatology 32: 405-412.

52. Bataller R, Brenner DA (2005) Liver fibrosis. J Clin Invest 115: 209-218.

53. Lima-Cabello E, Garcia-Mediavilla MV, Miquilena-Colina ME (2011) Enhanced expression of pro-inflammatory mediators and liver X receptor-regulated lipogenic genes in non-alcoholic fatty liver disease and hepatitis C. Clin Sci (Lond) 120: 239-250.

54. Kountouras J, Zavos C, Chatzopoulos D (2003) Apoptosis in hepatitis C. J Viral Hepat 10: 335-342.

55. Jacobson-Brown PM, Neuman MG (2001) Immunopathogenesis of hepatitis C virus infection: Th1/Th2 responses and the role of cytokines. Clin Biochem 34: 167-171.

56. Dinarello CA (2007) Historical insights into cytokines. Eur J Immunol 37: S34-S45.

57. Burgner D, Jamieson SE, Blackwell JM (2006) Genetic susceptibility to infectious diseases: big is beautiful, but will bigger be even better? Lancet Infect Dis 6: 653-663.

58. Clementi M, Di-Gianantonio E (2006) Genetic susceptibility to infectious diseases. Reprod Toxicol 21: 345-349.

59. Tuite A, Gros P (2006) The impact of genomics on the analysis of host resistance to infectious disease. Microbes Infect 8: 1647-1653.

60. Fanning LJ, Levis J, Kenny-Walsh EW (2001) HLA class II genes determine the natural variance of hepatitis C viral load. Hepatology 33: 224-230.

61. Hong X, Yu RB, Sun NX (2005) Human leukocyte antigen class II DQB1*0301, DRB1*1101 alleles and spontaneous clearance of hepatitis C virus infection: A meta-analysis. World J Gastroenterol 11: 7302-7307.

62. Aguilar-Reina J, Ruiz-Ferrer M, Pizarro MA (2005) The 670A-G polymorphism in the promoter region of the FAS gene is associated with necrosis in periportal areas in patients with chronic hepatitis C. JVHepat 12: 568-573.

63. Barrett S, Collins M, Kenny C (2003) Polymorphisms in tumour necrosis factor-alpha, transforming growth factor-beta, interleukin-10, interleukin-6, interferon-gamma and outcome of hepatitis C virus infection. J Med Virol 71: 212-218.

64. Persico M, Capasso M, Persico E (2006) Interleukin-10-1082GG polymorphism influences the occurrence and the clinical characteristics of hepatitis C virus infection. J Hepatol 45: 779-785.

65. Chuang JY, Yang SS, Lu YT, Hsieh YY, Chen CY, et al. (2009) IL-10 promoter gene polymorphisms and sustained response to combination therapy in Taiwanese chronic hepatitis C patients. Dig Liver Dis 41: 424-430.

66. Lazarus R, Vercelli D, Palmer LJ (2002) Single nucleotide polymorphisms in innate immunity genes: abundant variation and potential role in complex human disease. Immunol Rev 190: 9-25.

67. HInds DA, Kloek AP, Jen M (2006) Common deletions and SNPs are in linkage disequilibrium in the human genome. Nat Genet 38: 82-85.

68. Neuman MG, Bebhamou JP, Malkiewicz IM (2001) Cytokines as predictors for sustained responde and markers for immunomodulation in patients with chronic hepatitis C. Clin Biochem 34: 173-182.

69. Abbas Z, Moatter T, Hussainy A (2005) Effect of cytokine gene polymorphism on histological activity index, viral load and response to treatment in patients with chronic hepatitis C genotype 3. World J Gastroenterol 11: 6656-6661.