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Artículo de revisión

Hepatitis C

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Resumen

El virus de la hepatitis C (VHC) es el agente etiológico más común, concomitante con la transfusión sanguínea y con la hepatitis de la comunidad no-A, no-B, con una seroprevalencia mundial estimada de 1%. Este virus RNA se identificó en 1988 y hasta la fecha se reconocen seis genotipos. La infección por el VHC se vincula con una plétora de alteraciones inmunológicas y autoinmunitarias. Los mecanismos propuestos de su patogenicidad son: *1)* El VHC es directamente citotóxico, *2)* ocurre una reactividad citotóxica de células T, *3)* el alto promedio de mutaciones en la región hipervariable del genoma viral (la región Es/NS1), le permite al virus escapar de la respuesta inmunitaria humeral y celular del huésped, *4)* los monocitos y macrófagos infectados pueden contribuir al daño del hepatocito. El tratamiento farmacológico actual para la hepatitis C crónica es una dosis semanal subcutánea de interferón pegilado, en combinación con una dosis diaria de ribavirina, con una respuesta serológica sostenida de cerca del 55% de los pacientes infectados.

Palabras clave: hepatitis, patogénesis, tratamiento, virus.

Abstract

Hepatitis C virus (HCV) is the major etiological agent associated to blood transfusion and community acquired non-A, non-B hepatitis with an estimated worldwide seroprevalence of approximately 1%. This RNA virus was identified in 1988; until now six distinct major genotypes have been identified. HCV infection is associated with a plethora of immune and autoimmune perturbations. The proposed mechanisms of the pathogenicity are: *1)* HCV is directly cytotoxic; *2)* there is a cytotoxic T cell reactivity to HCV determinants; *3)* the high mutation rate in the hypervariable region of the viral genome (the Es/NS1 region) allows the virus to escape the host's humeral and cellular immune defense, and, *4)* monocytes and macrophages infected with HCV may contribute to the hepatocyte injury. The current standard pharmacologic treatment of chronic HCV is weekly subcutaneous peginterferon in combination with daily oral ribavirin, which results in sustained virologic response in approximately 55% of chronically infected patients.

Key words: hepatitis, pathogenesis, treatment, virus.

Etiology

Hepatitis C is an agent that persists in tissue for years by escaping the immune system, damaging its host while simultaneously being associated with autoimmune hepatitis as well as other putative autoimmune diseases.[1] Infection with hepatitis C virus (HCV) causes chronic hepatitis C (CHC) in at least 50% of patients.[2]

HCV is the major etiological agent associated to transfusion and community acquired non-A, non-B hepatitis with an estimated worldwide seroprevalence of approximately 1%.[3] Those at greatest risk for HCV infection are patients with history of intravenous drug use, and blood transfusion. Cross-sectional studies report a 1% to 3% lifetime risk for infection in sexual partners of patients with known HCV infection. The reported estimated risk for mother-to-infant transmission of HCV infection has varied widely, ranging from 0% to 20%. HCV transmission during normal household events is extremely uncommon.

In 1988 it was identified the linear, single-stranded RNA virus of the hepatitis C, with positive polarity consisting of 9,400 nucleotides and a single open reading frame that codes for a viral protein of approximately 3,000 amino acids.[4] Although six distinct major genotypes have been identified, recently numerous sub-species of HCV have been defined by nucleotide mapping. All are antigenically identical for the purpose of detection of the disease. The 5´end of the genome consists of an untranslated highly conserved region adjacent to the genes for various structural proteins such as the nucleocapsid core and the viral surface protein. On the other hand, the envelope proteins are encoded for a hypervariable region, which varies markedly from viral isolate to viral isolate and sometimes even within viral agents isolated from the same patient at different time periods during the course of infection (quasi-species); this is why no vaccine against HCV is available.

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Subtypes

HCV is the most variable virus among the hepatitis viruses. The hypervariable region of the virus genome codes for its envelope proteins. As a result, these proteins vary from isolate to isolate and even within the same patient studied across time.

Genotyping may be clinically important as different genotypes may have different clinical outcomes in terms of their disease activity, potential for chronicity, replication efficiency and response to medical treatment.

In the recently developed consensus system, the various HCV genotypes have been numbered in the order of their discovery using Arabic numerals starting with 1a and extending through 6a. Subtypes within a genotype are identified by lower-case letters that follow the major type classification.

Physiopathology

Because HCV-RNA can not integrate into the host's genome, it remains a mystery how HCV leads to the development of hepatocellular carcinoma. HCV is thought to be directly cytopathic for hepatocytes.

The HCV persists for decades in the infected host. The injury in most cases of HCV disease is of low grade and chronic, not severe, fulminating hepatitis due to HCV is rare.

The role of the immune system in HCV disease is unclear but we know that immune suppression accelerates the natural history of the disease. Also, we know that HCV infection is associated with a plethora of immune and autoimmune perturbations.

It is widely believed that the host's immune response to HCV envelope epitopes is the driving force for the numerous quasi species that exist and enable the virus to persist an immune response directed against it.

The immune response to HCV may include the development of rheumatoid factor, antinuclear antibodies (ANA), anticardiolipin, antithyroid and anti-liver/kidney/microsomal antibodies (anti-LKM), as well as HCV/anti-HCV immune complex formation and deposition, cryoglobulins that may explain the cause of mixed essential cryoglobulinemia, and has been associated with membranous and membranoproliferative glomerulonephritis.[5]

It has been established that HCV exist in plasma in two distinct forms: free virus and virus complexed to antibodies.[6] The latter form may be neutralized virus. The formation of neutralizing anti-HCV antibodies might prevent the spread of infection to neonates from infected mothers.

The proposed mechanisms of the pathogenicity are: *1)* HCV is directly cytotoxic, *2)* there is a cytotoxic T cell reactivity to HCV determinants and may also determine disease activity or outcome, *3)* the high mutation rate in he hypervariable region of the viral genome (the Es/NS1 region) allows the virus to escape the host's humeral and cellular immune defense, and, *4)* monocytes and macrophages infected with HCV may contribute to the hepatocyte injury caused by the virus by secreting cytokines that enhance liver cell injury.

HCV infected plasma cells and persistent HCV infection facilitate the expression of B cell associated immunologic processes leading to immunoglobulins production which have cryoglobulin and rheumatoid factor activity. HCV infection enhances the expression of HLA antigens on infected cells, the number of activated T lymphocytes within infected tissues and the presentation of autoantigens to both T and B cells.

Histological spectrum extends from normal histology to extensive inflammation with advanced fibrosis or cirrhosis.

Diagnosis

Out of people with known HCV infection, only 25% to 30% seek medical attention for symptoms attributable to HCV infection; however, many of these symptoms, such as fatigue, are nonspecific.[7] Current methods are not enough to identify all cases with active HCV infection and these "occult cases" are detectable only with HCV-RNA testing. HCV can infect cells other than hepatocytes, such as peripheral mononuclear cells, pancreatic cells, and salivary glands, as is the case of HBV.[8,9]

HCV may elevate liver enzymes only minimally or transiently, and serum transaminases may be normal in the setting of histologically proved cirrhosis.[10]

The detection of HCV-RNA using PCR (polymerase chain reaction) techniques is the most sensitive method for detecting HCV currently available. With this technique, HCV-RNA can be detected within a few days to few weeks of exposure to HVC, well before the appearance of any form of anti-HCV, and it persists throughout the duration of the infection. In chronic HCV infection, the virus may be detectable only intermittently.

Qualitative and quantitative PCR are possible using serum and liver tissue. Only at HCV-RNA levels lesser than

3.5×10^5 genome equivalents/mL of serum the qualitative assays are useful. A minus strand of RNA is produced from the RNA with the help of a RNA dependent RNA polymerase.

Most common diagnostic testing relies on identifying the presence of anti-HCV antibodies in the sera of infected patients using enzyme immunoassay (EIA) and recombinant immunoblot assay (RIBA) methodology. The sensitivity of second-generation HCV EIA appears to be approximately 80 to 90%, although there may be a high level of nonspecificity (as high as 50%) using confirmatory, second generation RIBA (RIBA-2) in low-risk populations.

The presence of anti-HCV antibodies by the highly sensitive and specific RIBA-2 in the presence of elevated serum transaminase levels is believed to be diagnostic of HCV infection, although false-positive results are known to occur. Third-generation EIA and RIBA assays improve sensitivity slightly, but do not improve specificity significantly.[10,11]

Liver biopsy in HCV-infected patients is useful for gauging disease severity and ruling out other causes of hepatitis. The characteristic morphological features of HCV infection include steatosis, lymphoid aggregation within the portal triads, and infiltration of the interlobular bile ducts with lymphocytes and plasma cells.[12]

Despite advances in the detection methods available for identifying cases of HCV, 5% of patients with chronic liver disease continue to have cryptogenic disease. Almost a half of the patients with cryptogenic hepatitis have been transfused.

Disease

Hepatitis C virus infections become chronic in more than 80% of the patients. CHC infection is a frequent cause of end stage liver disease and is associated with the development of both liver cirrhosis and hepatocellular carcinoma.

The mean time of development of chronic hepatitis C, cirrhosis and hepatocellular carcinoma is respectively 10, 21 and 28 years.

A major question is whether or not an association between autoinmmune hepatitis (AH) and CHC infection exists.

Patients with CHC have detectable autoantibodies, specially the liver kidney microsomal (LKM) autoantibody. Additionally, antinuclear (ANA) and smooth muscle antibodies occur at higher frequencies.

GOR, which is a naturally occurring pentadecapeptide, is an epitope that is readily recognizable by the host's cellular immune responses and there is a strong relationship between seropositivity for antibody to GOR and LKM antobodies and HCV infection.

A structural similarity between the target of these antibodies and proteins produced by the HCV appears most likely. As a result, an HCV infection can initiate an immune response to structurally similar host's antigens turning them into auto-antigens.

Treatment

It is essential to determine the precise relationship between HCV and autoimmunity before starting any treatment because interferon (IFN)-alpha may precipitate or exacerbate autoimmune disease symptoms; by the other hand, HCV-related autoimmune disease has been treated successfully with corticosteroids, azathioprine, and cyclophosphamide, although HCV viremia pesists and may worsen.

Essential HCV replication proteins are logical targets for anti-HCV therapy. A multifunctional enzyme, the NS3 is one of these putative essential proteins.

With IFN treatment, responders typically experience a rapid decline in their serum alanine-amino-transferase (ALT) level, but IFN can produce a deleterious effect in patients with a coexistent autoimmune disease.

Prospective randomized clinical trials have demonstrated that both recombinant and lymphoblastoid alpha interferon were effective in the treatment of chronic hepatitis C.

In a review of 52 randomized clinical trials of chronic hepatitis C[13] interferon (alpha-2a, alpha-2b, alpha-2c and lymphoblastoid [natural] interferon) initially induced ALT normalization in 1499/2927 patients (51.2%), but due to a high relapse rate (>50%), only 482/2218 (21.7%) still had normal ALT values three months after interferon therapy had been stopped. The long term response rate significantly increased with increasing weekly doses and with the duration of interferon therapy (r=0.25 and 0.38 with p<0.01, respectively). Correspondingly, the response rate was correlated most closely with the total dose of interferon given (r=0.49, p<0.001). The presence of cirrhosis is associated with markedly reduced short and long-term response to interferon.

Current therapy for infection with HCV involves treatment with alpha-interferon, alone or in combination with ribavirin. Such treatment is only effective for a minority of patients.[14]

Therapy with ribavirin leads to diminishment in serum aminotransferase concentrations in 50 to 60 percent of patients and, if given for 12 months, to some degree of histological improvement. Combination therapy of interferon alpha and ribavirin is most helpful in patients, with a higher rate of long-term response (40-77%).

A broadly effective antiviral therapy for the treatment of infections with hepatitis C viruses has yet to be developed. One of the approaches was the development and design of specific small molecule drugs to inhibit the proteolytic processing of the polyprotein.[15]

Peginterferon in combinations with ribavirin has become the facto standard of care for treatment of chronic HCV infection. In subgroup analysis, sustained virologic response was of 42% in patients infected with genotype 1 and was of 82% in patients infected with genotype 2 or 3.[16]

Specific cytokines elaborated during HCV infection have not been thoroughly elucidated, but interleukin-2 (IL-2), IL-4, IL-10, and interferon-gamma have been reported significantly elevated in HCV infected patients compared with normal controls.[17]

Liver transplantation is a well-accepted, life-saving, surgical treatment that is available at many different medical centers.[18] It is the only therapeutic option for the patient with end-stage liver disease for whom alternative medical and surgical treatments have been exhausted. Controversies still exist such as who are the best candidates for a liver transplant due to differing survival rates and the risk of recurrent disease.[19]

Examples of controversial indications include alcoholic liver disease, viral liver disease, and hepatic cancer.[18,19] Liver transplantation needs immune suppression and is associated with progressive HCV disease. Recurrent infection can jeopardize the donor liver as a result of a viral infection and is associated with multiple rejection episodes.

Many liver transplant recipients with and without overt clinical (biochemical) hepatitis are viremic. The majority (>95%) of those who are viremic pre-transplant will be viremic after transplantation. It is established that HCV infection most be treated before liver transplant.

The current recurrence rate of hepatitis C virus-related hepatitis is of 72% at 1 year. The incidence of new acquired HCV infection is of 20% at 4 years. Liver histology is essential to identify whether or not post-transplant hepatitis is present.

Conclusions

Hepatitis C virus infection is the most frequent cause of post-transfusion hepatitis and chronic viral hepatitis, which lead to the development of chronic liver disease, cirrhosis, and hepatocellular carcinoma. HCV infection is associated with a broad spectrum of autoimmune diseases, such as rheumatoid arthritis, lupus erythematosus, thyroiditis, autoimmune liver disease, etc.

Liver transplantation is the only therapeutic option for the patient with end-stage liver disease for whom alternative medical and surgical treatments have been exhausted. Although it is a well-accepted, life-saving and available at many different medical centers in the United States, surgical treatment is not a common procedure in Mexico.

Interferon alpha has successfully reduced viremia/ transaminitis, cryoglobulins, proteinuria and nephritis, but recurrent disease manifestations are frequent after discontinuation of therapy.

Current therapy for infection with HCV involves treatment with alpha-interferon in combination with ribavirin, but a broadly effective antiviral therapy has yet to be developed.

The current standard of pharmacologic treatment of chronic HCV is weekly subcutaneous peginterferon in combination with daily oral ribavirin, which results in sustained virologic response in approximately 55% of chronically infected patients. Side effects of interferon therapy include myalgias, fever, nausea, irritability and depression.[20]

Although it is clear that the presence of an antinuclear antibody does not adversely affect the outcome of interferon therapy, such patients should be carefully monitored while receiving interferon for the development of autoimmune diseases, such as thyroiditis, rheumatoid arthritis, psoriasis, and systemic lupus erythematosus.[21]

Given its antiviral response, it is speculated that interferons and their immunoregulatory effects play major roles in response to HCV infection. Recently it has been reported a new drug, the collagen-polyvinylpyrrolidone (clg-pvp) with immunoregulatory actions;[22] these properties could be a new option for the treatment of HCV infection, although clinical trials need to be done.

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