Acute Hepatitis C Virus Infection: Diagnosis, Pathogenesis, Treatment

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Abstract

Diagnosing acute hepatitis C is still difficult. The disease is frequently asymptomatic and there are no specific diagnostic tests. Most frequently, diagnosis is based on anti HCV antibodies serum conversion and, more rarely, on a double serum conversion (initially HCV-RNA undetectable by RT-PCR, subsequently positive and serum conversion for HCV antibodies determined by EIA and RIBA techniques). Evolution of HCV infection is determined by the intensity of immune response, type of secreted cytokines and persistence of specific HCV T lymphocytes response. Patients achieving viral clearance present an early, strong and multi specific T lymphocyte response. Spontaneous viral clearance rates are highly variable between 10-60%. It is currently recommended to delay start of treatment for 2-4 months after onset and this delay does not compromise chances of achieving sustained virologic response. It is necessary to repeat viremia 6 months -1 year after spontaneous viral clearance due to the possibility of viral replication restart.

There are currently no firm guidelines regarding treatment regimens, treatment duration and timing of its initiation. Monotherapy with high dose interferon α or peg-interferon for 6 months is recommended.

Although important progress has been achieved in acute hepatitis C understanding, research continues to improve treatment regimens and to clarify mechanisms of viral clearance.

Key words

HCV - acute hepatitis - immune response - diagnosis, treatment

Introduction

Since 1970, when non-A non-B hepatitis viruses were first recognized, until the early 90’s, when Houghton et al successfully cloned HCV, different interpretations regarding evolution and prognosis of HCV infection existed. Initially, non-A non-B hepatitis was considered by the majority of researchers as an asymptomatic disorder with minor consequences or even an unspecific aminotransferase elevation. Prospective follow-up of these patients revealed that around 20% of them developed cirrhosis. Once the HCV structure was identified and sensitive anti HCV antibodies detection tests were developed, it became possible to implement new retrospective – prospective HCV study methodologies. These allowed the testing of serum from infected patients, stored decades ago, followed by control and reevaluation of these patients. Retrospective–prospective studies yielded useful information regarding natural evolution of HCV infection. One of the first observations of these studies was that the spontaneous viral clearance rates (around 25%) after acute HCV infection were higher than previously reported (1). According to several authors (2,3), spontaneous serum conversion rates in children and selected adults may be as high as 45% and 55%, respectively. Another important finding of the retrospective – prospective studies was that incidence of cirrhosis after 20 years was lower than 15% (sometimes even lower than 5%) and that there were minimal differences in mortality rates between HCV infected patients and non-infected subjects at 20 years. The ideal study of the natural history of HCV infection should have a well defined infection onset moment, a single source of infection, a large number of patients included, with prospective, complete and long term follow-up. Such a study is difficult to set up because acute HCV infection is rarely diagnosed and epidemics with known sources are unusual in present times (1).

Epidemiology

Epidemiology of acute HCV infection has significantly changed since the introduction of HCV screening in blood
banks. In industrialized countries, a dramatic decrease of post-transfusion infections has been recorded, residual risk being around 1/127,000 blood donations (4). As a result, the majority of cases in clinical practice nowadays are caused by use of intravenous drugs and much rarely by non-parenteral exposure (sexual contact or medical and cosmetic procedures) (5) and perinatal transmission (1). It is estimated that in the USA, more than 60% of new HCV infections are caused by intravenous drug use.

**Diagnosis**

There are a number of causes for which diagnosing acute HCV infection is still problematic. First of all, there are non-specific diagnostic tests, and serum markers currently used cannot differentiate between an acute infection and an exacerbation of a chronic HCV infection (5,6). Anti HCV IgM determination has not proved useful for diagnosing acute HCV infection because these antibodies can be present – in similar concentrations – both in acute and chronic infection (7). Acute HCV infection cannot be diagnosed based on clinical signs only, because infection is often asymptomatic or with non-specific low-intensity signs and is rarely recognized based on these criteria.

An exception is the early diagnosis of acute hepatitis C virus infection through systematic screening in asymptomatic patients exposed to known risk factors (8).

Currently, diagnosis of hepatitis C virus infection is based on documented anti HCV antibodies serum conversion (9). A small proportion of acute HCV infections (and chronic infections as well) are serum negative as determined by ELISA (Enzyme Linked Immuno Sorbent Assay). This can occur in patients with impaired immunity, which cannot generate a detectable level of anti HCV antibodies or in whom antibody production is delayed. Another situation is viral clearance, which can occur in the absence of antibody production or can be associated with a rapid loss of them (10). In these cases, acute HCV infection must be confirmed using RT-PCR (reverse-transcriptase polymerase chain reaction). HCV-ARN assessment must also be done if anti HCV antibodies are not detected but there is a high suspicion of infection (7).

HCV-RNA detection by a sensible method when anti HCV antibodies tests are negative, suggests an acute C virus infection, especially when it is followed by anti HCV serum conversion (4,11).

As testing of viral blood levels is expensive and it is neither sensitive nor specific for acute infection diagnosis, it is not used as a screening test, especially in areas with low infection prevalence (7).

A unique characteristic of acute HCV infection, probably caused by the possibility of spontaneous clearance, is the ‘variability’ of HCV-RNA levels, which can go from several hundreds IU to more than 1,000 000 IU/ml, very low levels being frequently encountered. Some patients may even have several negative PCR tests. These large fluctuations in HCV-RNA levels can be used to differentiate between acute and chronic infection; in the latter case, HCV-RNA levels are very stable and do not change with more than 1 log in a given patient (6).

Repetitive HCV-RNA assessments are mandatory due to the fact that in acute infection, which evolves into chronic infection, there may be a period of months or years in which aminotransferase levels are normal (or close to normal values) and direct markers of HCV infection (qualitative or quantitative determination of HCV-RNA and of core antigen) may fluctuate below the detection limit. Performed by using sensitive methods (TMA = transcription mediated amplification), these assessments may eliminate the false suggestion of healing when, in fact, the patient is developing chronic infection. Using the core antigen in these cases is not recommended due to its lower sensitivity compared to nucleic acid detection tests based on TMA (4).

Another useful test in diagnosing and monitoring patients with HCV infection is determination of core antigen. This is one of the best ‘conserved’ products of viral genome and in fact it is the HCV capsid, formed by core protein polymerization. Using EIA techniques, it can be detected and quantified in serum. The core antigen level (in pg/ml) is correlated with HCV-RNA level and is estimated that 1 pg/ml core antigen is equivalent with 8,000 IU/ml HCV-RNA, with small variations between patients. The current versions of EIA tests for core antigen do not detect it when HCV-RNA is below 20,000 IU/ml, which limits their use in practice (11).

Using core antigen determination as a surrogate marker of HCV replication is based on the fact that, before serum conversion, the core antigen can be detected 1-2 days later than HCV-RNA; afterwards, the core antigen and HCV-RNA kinetics are parallel.

Although some preliminary studies suggest a good correlation between serum levels of HCV-RNA and core antigen levels both in untreated and in patients treated with interferon or in patients with acute infection, further studies are required to establish the role of core antigen in the diagnosis and monitoring of HCV infected patients (11,12).

In patients with suspicion of acute HCV infection without documented serum conversion, some authors (9) advise seriate determinations of anti HCV antibodies levels; to detect anti HCV antibodies, 3rd generation ELISA tests have been used and their presence has been documented by S/CO ratio (signal/cut off); the presence of antibodies specific to some HCV proteins has been also determined using RIBA (Recombinant Immunoblot Assay) tests. Using as controls, patients with chronic HCV infection with acute exacerbations, the authors concluded that in acute HCV infection, anti HCV antibodies levels (S/CO ratio) become higher and a certain RIBA pattern emerges (serum conversion from negative/ undetermined to positive tests).

Although rarely encountered in clinical practice, documented anti HCV serum conversion in the presence of a positive HCV-RNA test and elevated aminotransferase levels is the gold standard for diagnosis (4).

After exposure, HCV-RNA becomes detectable in serum
after 7-14 days, followed by aminotransferase elevation and later (after 4-10 weeks) by antibodies’ presence (4).

**Pathogenesis**

The immune response has a unique role in the pathogenesis of viral hepatitis because it contributes both to viral infection control and healing as well as in developing chronic infection and liver cirrhosis. HCV is a non-cytopathic hepatotrop virus that induces acute or chronic liver disease and interacts in a complex way with the immune system (13).

The immune response (innate and adaptive) represents the first line of defense against viral replication; on its part, HCV has complex mechanisms to elude this immune response (14).

Interactions between HCV and host immune response in the first weeks after exposure may substantially influence the subsequent evolution and the prognosis of infection (15).

One-to-two weeks after exposure, HCV-RNA can be detected in serum and it quickly replicates, reaching serum levels of around 10<sup>6</sup> copies/ml (10,15). However, immunology studies showed a delay of the cellular adaptive immune response of 1-2 months (15) and of the humoral response of 2-3 months (13). These observations led to the hypothesis that HCV manages to surpass the adaptive immune response. This hypothesis is backed up by the rarity of symptomatic C virus infections, as we know that clinical signs and especially jaundice are caused by liver injuries mediated by T lymphocytes (13).

Another observation is that in HCV infection, the adaptive immune response seems to ignore significant viral levels for several weeks while in HBV infection the limited HBV antigen levels (in the early stages of infection) seem to be responsible for delaying the adaptive immune response (15).

After the first weeks from exposure, the initial (rapid) peak of viral replication is followed by a period of 4-6 weeks during which HCV-RNA may slightly elevate or remain stable, in the absence of specific HCV B and T lymphocytes and liver inflammation induction (10,15).

Serum aminotransferase levels begin to rise 2-8 weeks after exposure, and at 8-12 weeks, when their levels reach the maximum value, HCV-RNA levels diminish.

Anti HCV antibodies presence is variable, becoming detectable at the time of aminotransferases peak, later or not at all.

Viral clearance can occur before a measurable humoral response or even in its absence; therefore, there is a small proportion of patients which can have negative EIA tests for anti HCV antibodies during the acute phase and heal without developing any detectable serologic marker of infection (6).

More frequently, antibodies’ levels fall down in time after the viral clearance and may even disappear at 10-20 years after healing; this situation is encountered in 7-40% patients with spontaneous clearance, and those have no serologic marker of previous infection (6,10).

Viral clearance from the liver and possibly from other pools takes more time than the serum clearance – hypothesis sustained by the recurrence of viremia after several months of undetectable values.

At the present time, there is a debate whether HCV is eventually completely eradicated (13).

**Innate immune response**

The first mechanism of host defense against HCV infection is represented by the innate immune response. This consists of endogenous secretion of interferon and NK (natural killer) cells.

Animal studies show that HCV causes early alterations in the expression of several hepatocytic genes, especially in those related to the response to interferon type 1 (2'-5' oligoadenylate synthetase, double stranded RNA dependent protein kinase (PKR) and Mx protein) (6).

In acute phases of HCV infection, interferon 1 expression is one of the early manifestations of the innate immune response.

Interferon type 1 (α and β) represents the first line of host defense against infections and has antiviral and immunomodulation effects (15).

The mechanisms of action of interferon type 1 include:

1. down regulation of protein synthesis of the infected cells by inducing cellular protein kinases;
2. increased expression of major histocompatibility (MHC) genes on the antigen presenting cells and target cells;
3. inhibition of viral replication by activating Mx proteins or 2'-5' oligoadenylate synthetase;
4. up regulation of natural killer (NK) cells, dendritic cells (DC) and CD8 lymphocytes activity;
5. induction of cell death by activating molecules involved in apoptosis.

Although HCV is sensible to interferon in vitro, recent data suggest that the virus has developed various strategies to interfere with the antiviral activity of interferon. Thus, HCV can reduce the intracellular production of interferon α by the inhibitory effect of some non structural proteins (NS3-NS4A, NS5A) with some regulating factors of interferon production. Proteins from viral envelope (E2) and also NS5A inhibit the activity of double stranded RNA dependent protein kinase (PKR) in vitro, which is one of the antiviral proteins stimulated by interferon (14). The consequence of these interventions is that the initial production of interferon type 1 may slow down but not block the viral replication (15). Another explanation may be that although HCV induces efficiently early interferon secretion, it is relatively resistant to its action (6).

Viral proteins also influence the activity of NK cells. Thus, proteins from HCV envelope bind to the surface of NK cells blocking their activation, cytokine secretion and cytotoxic activity (14).
In vitro studies showed that NK cells from patients with HCV infection (but not from healthy individuals) have a lower capacity to activate the dendritic cells (13).

**Dendritic cells and their role in controlling the viral infection**

Dendritic cells constitute a heterogeneous population of antigen presenting cells, playing important roles in antiviral immunity. They connect innate and adaptive immune responses. Signals from innate immune system (production of interferon type 1, interactions with NK cells) determine the maturation of dendritic cells. These are essential for launching antigen specific immune response. The role of the dendritic cells is to present the antigens to CD4 and CD8 lymphocytes (14).

After the stimulation realized by mature dendritic cells, CD8 (and also CD4) T lymphocytes proliferate intensely (15).

**Adaptive immune response**

**Cellular immune response**

Currently, it is generally accepted that the intensity and persistence of specific HCV T lymphocytes response as well as the secreted cytokine profile determine the evolution of HCV infection.

It has been demonstrated that an early, strong, polyclonal and multi specific (against several viral epitopes) response from CD4 and CD8 T lymphocytes is correlated with viral clearance (6,7,16).

Secreted cytokine profile may also influence the evolution of HCV infection. Th1 cytokines stimulate cytotoxic CD8 lymphocytes while Th2 cytokines stimulate antibody production. Thus, a Th1 cytokines secretion response has been associated with healing after acute infection (4,17).

If the immune response is late, less efficient (of lower intensity), against a lower number of viral epitopes and does not persist for a sufficient period, HCV infection tends to become chronic. Also, patients developing chronic infection have a Th2 cytokine secretion (6,7).

Data regarding the persistence of T lymphocyte response after acute infection is controversial and suggests that while CD4 T lymphocyte response persists several years after acute infection, CD8 T lymphocyte response fades in time (14).

Currently, there is no explanation why some responses are more efficient than others and if HCV persistence is responsible for reducing T lymphocyte response or vice versa (10).

**Humoral immune response**

HCV specific antibodies become detectable in serum after the onset of cellular immune response and aminotransferase elevation (6).

The first detectable antibodies in serum, HCV specific, are those that target NS3 region (anti c-33 antibodies) and core (anti 22c or anti capsid antibodies). Later, region NS4 specific antibodies and those directed against envelope proteins (E1 and E2) appear (7).

Unlike HBV infection, in which surface antigen specific antibodies have neutralization capacity, in HCV infection a protective role of anti HCV antibodies has not been proven.

Furthermore, in HCV infected patients, specific antibodies appearance is variable: early antibodies after exposure do not appear as in HBV infection, in which HBe IgM antibodies appearance is a marker of recent infection and, in some cases of HCV infection, specific antibodies may not appear at all.

There are other important differences regarding the immune response between HCV and HBV infection: anti HCV antibodies levels are lower than HBV antibodies levels by at least 2 log and the profile of anti HCV antibodies is narrower than that in HBV infection. Also, anti HCV antibodies do not persist for the rest of the life, disappearing at 10-20 years after healing.

Interesting observations about the role of the immune response have been made by evaluating hepatitis C evolution in patients with a deficit in antibody response.

Although the number of studies is limited, spontaneous resolutions have been noted in HCV infected children with agammaglobulinemia, which demonstrates that controlling HCV infection is possible regardless of the antibody response (7).

Currently, the mechanisms of HCV persistence, despite specific antibodies and cellular immune response occurrence, are still not completely known.

**Viral eradication, viral recurrence**

Although the majority of researchers consider that the patients cured after acute hepatitis C achieved viral eradication, a series of recent papers (18) have argued this concept. Using PCR tests, sequences of RNA have been identified in serum and/or monocytes from peripheral blood of some patients at 5 years since the spontaneous healing of acute hepatitis. In these patients, negative chains of HCV-RNA have been identified in the majority of peripheral monocytes, demonstrating that intermediary replicative forms of HCV may persist for many years after apparent healing. Similar data have been obtained from patients with sustained virologic response after antiviral treatment.

Although further confirmation is required, these data have major clinical implications, especially in cured patients in which HCV could reactivate if they would receive immune suppressor treatment – just like in occult HBV infection (4).

Another important aspect is represented by recurrence of viremia observed in patients in whom HCV-RNA tests have been negative for 4 months after aminotransferase normalization. Because disappearance of specific CD4 T lymphocyte response preceded HCV recurrence, this observation indicates that HCV is controlled but not completely eradicated in the first months after the (clinical) healing of acute hepatitis (13).
Mechanisms of viral escape

Unlike HBV, HCV causes chronic infection in the majority of cases. The exact mechanisms by which HCV escapes from the immune response are not completely elucidated.

One of the most important mechanism of escape is represented by mutations in viral sequences. There are 6 HCV genotypes currently known (and many viral subtypes) and in a given host HCV can be found as a “mixture” of sequences with similar structures, named quasispecies.

The existence and the nature of quasispecies are considered mechanisms of HCV escape from immune response. The nature of quasispecies, the high replication rate and the lack of proof reading capacity of HCV polymerase, contribute to the rapid diversification of viral population. The apparent delay in the onset of adaptive cellular and humoral immune response facilitates this process; thus, mutants of immune escape can be quickly selected from pre-existing quasispecies population when adaptive immune response does appear (13).

Mutants of HCV escape affect cellular immune response at several levels: antigen processing, MHC binding and stimulation of T lymphocytes receptors.

Even if HCV mutant does not represent the dominant viral sequence, it can still contribute to the down regulation of T lymphocyte response against the wild virus.

Studies that followed the evolution of quasispecies in patients with post transfusion acute C hepatitis concluded that spontaneous resolution of infection was associated with a narrower genetic diversity of viral variants while patients developing chronic hepatitis presented a marked genetic diversity (19). Thus, population dynamics in early stages of HCV infection may better predict if infection is going to be self limited or it will become chronic infection.

Humoral immune response exerts a selective pressure on viral population leading to an increase in complexity and diversity of quasispecies, allowing escape from the immune control and HCV persistence. This hypothesis is backed up by observations in chronic HCV infected patients with primary immune globulin deficiencies, in whom the number of mutations in hyper variable region HVR1 was significantly lower, compared to those in immune competent patients.

Other mechanisms of immune escape were proposed, implicating viral proteins. Immune modulator effect of some HCV proteins on the immune system cells (innate and adaptive) is not fully understood but it has been demonstrated that core proteins affect both T lymphocyte differentiation and their effective functions.

HCV core proteins (specific sequences in their structure) bind to the complement receptors on the macrophages and T lymphocytes surface, causing a decrease in IL12 (interleukin 12) production by macrophages and reducing T lymphocyte proliferation, IL2 and interferon α production by the latter. Reduced IL2 secretion determines an incomplete maturation and differentiation of specific lymphocytes (20).

HCV proteins may also affect the function of dendritic cells, reducing their cytokine secretion (especially interferon type 1 and 2 and IL12) and their differentiation (20).

Non structural HCV proteins (NS5A) induce pro inflammatory cytokine expression (IL8) associated with the inhibition of interferon action both in vitro and in vivo (21).

These effects of HCV proteins on the immune response represent possible mechanisms of viral persistence and, as a result, of chronic liver disease (4).

Evolution of infection with antiviral therapy

Studies of viral kinetics showed that during the treatment of HCV infection both mechanisms of action of interferon α – inhibition of viral replication and immune modulating effects – are involved in achieving viral clearance.

In the first phase, which lasts 1-2 days, a marked decrease in HCV-RNA is recorded, due to antiviral effects of interferon α which eliminate circulating virions. In the second phase, from the second day to 14-28 days, small variations of HCV-RNA in serum are recorded; this phase marks the debut of viral clearance from infected hepatocytes. In the third phase, HCV-RNA levels decrease again, but with a smaller rate compared to the first phase. It is currently considered that the latter phase comprises the restoration of cellular immune response which leads to viral clearance from hepatocytes (22-24).

Studies of viral kinetics revealed important information regarding the immune response during interferon treatment. Thus, it has been noted that specific HCV CD4 T lymphocyte response increases significantly during antiviral therapy, unlike that of CD8 T lymphocytes which showed minimal changes. Some authors sustain the existence of an association between the recovery of CD4 lymphocyte response and virologic response to treatment (25,26). This recovery of specific CD4 T lymphocyte response during antiviral treatment – also noticed in chronic HVB and HIV infection – may be due to the reduction of the suppressor effect of high viremia on T lymphocytes associated with redistribution of CD4 T lymphocytes from the inflammatory site into the blood stream.

As previously shown, a strong immune response from CD4 T and T cytotoxic lymphocytes is associated with spontaneous viral clearance.

Nevertheless, CD4 T lymphocyte response during antiviral treatment is different in chronic hepatitis from self limited acute disease. In chronic hepatitis, the response from these cells is reduced and variable and usually does not persist in time (27).

On the other hand, some authors (28) consider that there is no long term response from the CD4 T lymphocytes against HCV in patients with acute C hepatitis in whom viral clearance has been achieved after interferon therapy. They also consider that CD8 lymphocytes are more important, suggesting that their level correlates with the viral clearance and with the evolution of acute HCV infection.

Persistence of CD4 T lymphocytes is essential for achieving a durable HCV-RNA negativeness and for protection against a secondary HCV infection.
CD₈ T lymphocytes, especially the specific memory CD8 T lymphocytes, play a protective role against persistent HCV infection in the case of re-exposure to the virus. Furthermore, more and more data sustain the hypothesis of specific HCV CD₈ T lymphocytes induction after interferon α therapy (28).

In conclusion, interferon therapy ‘strikes’ HCV by two different mechanisms: breaking of the relative interferon resistance of the virus and partial restoration of antiviral cellular immune response (27).

Natural evolution of acute HCV infection

As we have shown above, natural evolution of acute HCV infection is variable. It can evolve to spontaneous viral clearance (Fig.1) or into chronic infection (Fig.2).

Acute infection is frequently asymptomatic and fulminant liver failure is very rare. It evolves into chronic hepatitis in 50-84% cases – these variations being partially explained by the HCV pattern of transmission, viral factors and host capacity to initiate a strong cellular immune response to eliminate the virus (29).

Treatment

Regarding the treatment of acute C hepatitis, there are currently more questions than answers: which patients should be treated (symptomatic or asymptomatic), what is the optimal moment to initiate treatment (immediately or after a while to allow for spontaneous clearance), what treatment regimen should be used and for how long (30).

Besides difficulties arising from the variable evolution of infection from one individual to another, studies of antiviral treatment of acute C hepatitis have some limits: small number of patients included, heterogeneous population and different therapeutic regimens and definitions of an efficient response (31). Despite these difficulties, several important observations emerge from those studies.

One of the conclusions refers to post exposure prophylactic treatment. Due to the low infectivity rate of HCV (risk of parenteral transmission after accidental needle puncture being around 3%) (32), high rates of successful treatment in acute hepatitis and slow progression of hepatitis C, there are currently no data to justify prophylactic (post exposure) administration of interferon (8,29).

Another important observation refers to delay of treatment initiation because 15-20% of patients with acute C hepatitis achieve permanent spontaneous viral clearance, which demonstrates that HCV can be controlled by the intervention of immune mechanisms (27). It is considered that a period of 12 weeks from the clinical onset before starting antiviral therapy is enough to allow for spontaneous viral clearance (32).

Furthermore, a recent meta analysis confirmed that delaying the treatment 2-3 months after establishing the diagnosis does not compromise the rate of sustained virologic response (6).

Although important progress has been made in acute hepatitis C treatment, currently there are no firm guidelines regarding optimal treatment regimens, duration of therapy and timing of treatment initiation.

It seems that associating ribavirin to interferon treatment does not increase the rates of virologic response and its adverse reactions are important (30).

Some authors (34) suggest that an initial induction with high doses of interferon leads to higher response rates (90-100%) compared to therapeutic regimens which use interferon 3 times a week. Regimens used included standard α2b interferon 5MU daily for 4 weeks followed by doses of 5 MU 3 times / week for 20 weeks (30). Japanese authors propose a short treatment (4 weeks) with interferon α i.m. 6 MU daily, starting in early phases of acute HCV infection (35). This regimen yields high rates (87%) of sustained virologic response.

There are a number of recent studies that indicate that monotherapy with pegylated interferon (1.5 μg/kg) for 24 weeks has a similar efficacy as standard interferon treatment, achieving rates of sustained response of around 95% (20,26,28,40).

Although there are no well defined predictive factors to
evaluate progression from acute to chronic infection, the majority of authors agree that icteric patients have a favorable evolution compared to asymptomatic patients, with higher chances of achieving spontaneous viral clearance (29,30). Some authors consider that female gender is associated with higher rates of viral clearance (40% in women compared to 19% in men) (36). It has been observed that a reduction of genetic diversity of HCV quasispecies leads to a homogeneous viral population, which is a characteristic associated both with spontaneous viral clearance and with that obtained in patients with sustained virologic response to interferon (19,37).

Prognosis

To evaluate long term prognosis in patients with acute hepatitis C, a period of 6 months follow-up is required after spontaneous viral clearance. There are at least two reasons for this recommendation: one is the re-start of viral replication which can occur in the first 6 months after spontaneous viral clearance, being associated with proliferation failure of HCV specific CD4 T lymphocytes (encountered in viral clearance stage) (38). The second reason is that in many patients with acute hepatitis C, a transient negativation of HCV-RNA during recovery after acute phase has been noted, without any relation to the evolution towards chronic state (31). For these reasons, it is currently recommended to repeat HCV-RNA determinations in the follow-up phase.

Although there are controversies regarding prognostic factors, symptomatic and jaundiced patients develop chronic disease much rarely than asymptomatic ones. Favorable prognostic factors include monophasic aminotransferase pattern and the magnitude of their peak during acute disease (the higher this is, the lower the persistence probability). Age and gender seem to influence rates of evolution to chronic state, younger patients and women having lower rates (10). Source of infection and scale of exposure influence rates (10). Race seems to be important too, black people having higher rates of evolution to chronic state, post transfusion hepatitis having the highest risk. Amongst unfavorable prognostic factors, the most important are excess alcohol consumption and concomitant HBV and HIV infection (12).

In the absence of treatment guidelines for these patients, it is currently recommended that treatment should be initiated in patients for whom benefits outweigh the risks and management of these patients should include psychological support (30).

In conclusion, because the disease is frequently asymptomatic and there are no specific tests to diagnose acute HCV infection, it is rarely recognized and diagnosed.

Although there are currently no firm guidelines regarding therapeutic regimens and timing of treatment, available data recommend monotherapy with interferon or with peg-interferon for 4-6 months (6,12,39). Treatment should be instituted in patients with positive HCV-RNA and elevated aminotransferases after this period. This prevents undue treatment of patients which achieve spontaneous viral clearance, without compromising the efficacy in preventing evolution to chronic state.

References