

ACUTE HEPATITIS C VIRUS INFECTION

ŪMINĖ VIRUSINĖ HEPATITO C INFEKCIJA

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SUMMARY

KEY WORDS: acute infection, hepatitis C virus (HCV), T cells, immune response, interferon

Hepatitis C virus infection is a global public health problem. Up to 3% of the world's population is infected with HCV. Acute HCV infection is usually asymptomatic and therefore rarely diagnosed disease. Only a small number of acutely infected persons clear the virus spontaneously, while the majority of newly infected patients progress to chronic hepatitis such that HCV infection is now the leading cause of cirrhosis, hepatocellular carcinoma and liver transplantation in the Western world. Recognition of acute HCV infection and prevention the evolution to chronic disease is a necessity. Currently there are no specific tests distinguishing acute from chronic infections. However, significant advances have been made in understanding acute phase of the disease. This review provides an overview of recent knowledge of the etiology, changing epidemiology, diagnosis, natural course, immunology as well as the current antiviral treatment options for acute hepatitis C.

SANTRAUKA

REIKŠMINIAI ŽODŽIAI: ūminė infekcija, hepatito C virusas (HCV), T ląstelės, imuninis atsakas, interferonas

Hepatito C virusinė infekcija yra aktuali visuomenės sveikatos problema. Hepatito C virusu užsikrėtę apie 3 proc. pasaulio gyventojų. Ūminė hepatito C infekcija dažnai yra besimptomė, todėl retai diagnozuojama liga. Tik nedaugeliui ligonių ūmi infekcija išnyksta spontaniškai. Daugumai naujai užsikrėtusių šiuo virusu liga įgyja lėtinę formą, kuri šiuo metu yra svarbiausia kepenų cirozės, hepatoceliulinės karcinomos ir kepenų transplantacijos priežastis išsivysčiusiose pasaulio šalyse. Ūminės hepatito C infekcijos anksčiau diagnostika yra būtinas veiksnys užkertant kelią ligos progresavimui. Dažnai sunku diferencijuoti ūmų hepatitą C nuo lėtinio paūmėjimo, nes nėra specifinių ūminio hepatito C diagnostikos kriterijų. Atliekami moksliniai tyrimai suteikia galimybę geriau suprasti šios ligos eigą. Straipsnyje apžvelgiami pastarųjų metų duomenys apie ūminės virusinės hepatito C infekcijos etiologijos, epidemiologijos, diagnostikos, natūralios eigos, imunologijos, taip pat antivirusinio gydymo ypatumus.

BACKGROUND

Hepatitis C virus (HCV) is a major global health-care concern. An estimated 170 million people are infected with HCV worldwide [1, 3]. Of those individuals exposed to HCV, up to 80% develop a chronic infection leading to the development of progressive liver pathology, including fibrosis, cirrhosis and hepatocellular carcinoma [1-3, 7]. Acute HCV infection

is usually subclinical and rarely diagnosed. A minority of those acute HCV cases have self-limited disease, whereas the majority go on to chronic infection [2]. Treatment response rates during the acute phase are significantly higher than those observed during chronic infection [5, 6, 13]. However, viral and host factors responsible for these improved response rates and overall – for HCV viral persistence and spontaneous

clearance remain unclear. Understanding of mechanisms associated with resolution of HCV infection is critical to the development of more effective treatment and prevention strategies. Both from the clinical and research perspectives it is essential to recognize acute hepatitis C and to understand its clinical, laboratory and immunological aspects.

ETIOLOGY OF ACUTE HCV INFECTION

Hepatitis C virus is a small, enveloped RNA virus belonging to the Flaviviridae family, genus Hepacivirus. The HCV genome is a single-stranded RNA molecule of positive polarity and has a length of approximately 9600 nucleotides. It contains a long open reading frame encoding a polyprotein, flanked by 5' and 3' non-translated regions essential for the translation of virus protein and genome replication. HCV genome does not enter the nucleus of infected cells. Once inside the cytoplasm HCV RNA is directly translated through an internal ribosomal entry site in the 5' non-translated region. The translated polyprotein is co- and post-translationally processed by host-cell and virus encoded proteases into structural and non-structural proteins [1, 2, 4, 7, 8, 11] (Figure). Following synthesis and maturation, non-structural proteins and

viral RNA form replication complexes, that catalyse the transcription of negative-strand RNA intermediates from which new positive-strand RNA molecules are generated. The genomic RNA is packaged into new viral particles, which are released via the vesicular secretory pathway [1]. A careful analysis of viral dynamics predicted a virion half-life of 3-5 hours and a high clearance and production rate of up to 10^{10} - 10^{12} particles per day [1, 11].

An important feature of HCV replication is the rapid generation of virus variants. Phylogenetic evaluation of HCV sequences recovered from multiple geographic regions defined at least six major genotypes (1-6) and a large number of subtypes (1a, 1b, 2c, etc). HCV genotypes differ from each other by up to 30%, and subtypes - by 10-25% in nucleotide sequence [1, 4]. Despite the sequence diversity of HCV, all genotypes share an identical complement of co-linear genes of similar or identical size in the large open reading frame, and are likely undergo the same post-translation modifications. HCV genotypes 1, 2 and 3 are the most frequently encountered viral types worldwide. Subtypes 1a and 1b are widely distributed in the United States and Europe. In contrast, genotype 4 infections are the commonest throughout the Middle East, while genotypes 5 and 6 have been reported in

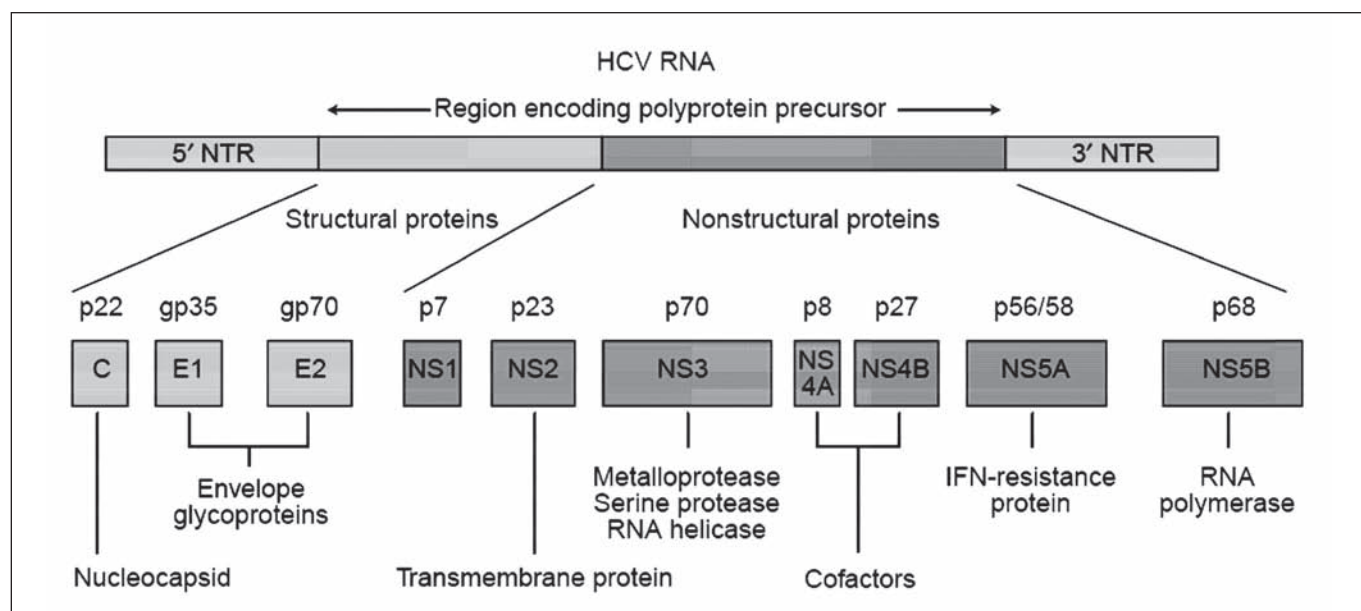


Figure. HCV genome organization, polyprotein cleavage products and putative functions of viral proteins [M.Anzola and J.J.Burgos. Expert Reviews in Molecular Medicine. 2003; 5:1-16].

The viral genome contains a large open reading frame encoding a polyprotein precursor that is proteolytically cleaved into a set of distinct products. The structural proteins C, E1, E2 and p7 (a protein of unknown function) are liberated from the polyprotein by cellular signal peptidases. Non-structural proteins include NS2, NS3, NS4A/B and NS5A/B, which are involved in the polyprotein processing and viral replication. The junction between NS2 and NS3 is cleaved by the NS2/3 metalloprotease. All other cleavages are mediated by the NS3/4A serine-type protease complex. Approximate sizes (kDa) of the mature proteins and glycoproteins are indicated. NTR, non-translated region; C, core protein; E, envelope protein; NS, non-structural protein; IFN, interferon; p, protein; gp, glycoprotein.

South Africa and Southeast Asia [1]. Genotype identification is clinically important, because types 1 and 4 are more resistant than genotypes 2 and 3 to the current chronic HCV standard care, pegylated interferon- α and ribavirin combination therapy [1, 68, 92].

Within a patient HCV does not exist as a single entity, but rather as a swarm of microvariants of a predominant 'master sequence', a phenomenon that has been referred to as quasispecies. The rapid evolution of sequence variations is primarily due to the lack of proofreading activity of the viral RNA-dependent RNA polymerase [2]. The highest nucleotide mutation rate occurs in the hypervariable region 1 (HVR-1) of the HCV E2 protein, however, such mutations can occur at any position within the viral genome [7]. In a study by Farci and colleagues [9], while a lack of viral mutation was associated with disease resolution, the evolution of sequence changes in the HVR-1 region during acute infection in humans was associated with the development of HCV persistence [7, 10]. Hence, the quasispecies may contribute to the viral persistence by permitting selection of variants that evade the host immune response [2, 7].

CHANGING EPIDEMIOLOGY OF ACUTE HCV INFECTION

HCV is endemic worldwide, although there is a large degree of geographic variability in its distribution. Countries with the highest HCV prevalence are located in Africa and Asia [68]. Egypt has the highest reported seroprevalence rate, 22%. In contrast, in most developed nations, the HCV prevalence is typically 1% to 2% in the general population [4]. HCV infection occurs among persons of all ages. In Europe, and particularly in the Mediterranean countries, the prevalence of HCV infection increases in parallel with age while in the United States it is common in persons 30-49 years old [11, 67]. A major determinant of the future burden of disease is the past and present incidence of infection. The Centers for Disease Control and Prevention (CDC) estimated that the annual incidence of acute HCV infection in the United States decreased from an average of 230 000 new cases per year in the 1980s to 38 000 cases per year between 1987 and 1997. This 80% reduction in incidence rate was attributed to a decrease in the numbers of transfusion-associated infections after the introduction of an all-volunteer donor system and widespread screening of blood donations in the early 1990s [2, 3, 6]. The incidence of registered cases of acute hepatitis C in different countries in

Eastern Europe varied between 2.2 and 9.0 per 100 000 population in 1997 [94].

Most developed countries have accumulated evidence that the predominant source of new HCV infections within their borders over the past few decades is injection drug use [4, 11, 12]. In countries such as the USA and Australia, despite widespread availability of educational and syringe-exchanged programs, injection drug use accounts for 68% and 80% of current infections, respectively [94]. In the developing world, unsafe healthcare procedures and transfusions are likely to be the major modes of transmission. Unscreened, remunerated donors, also contaminated injection equipment, injections outside the medical settings given by non-professionals appear to be essential risk factors for HCV infection throughout the developing world. In Egypt, the country with the highest reported seroprevalence in the world, transmission has been attributed to contaminated glass syringes used in nationwide schistosomiasis treatment campaigns in the 1970s [1, 3, 4].

The relative importance of other routes of infection has changed little over time. These consist of unprotected sex with an infected partner or with multiple partners, occupational and perinatal exposure, nosocomial infections, unsafe tattooing, body-piercing and acupuncture. No recognized source of infection can be identified in around 10-30% of infected patients, however a large proportion of this group has low socioeconomic background often associated with high-risk behavior, such as contact with a sexual partner or house-hold member who used intravenous drugs [1, 11].

Several cofactors have been associated with the higher rates of chronic outcome among those infected with HCV. These cofactors are male sex, older age at acquisition of HCV infection, obesity, human immunodeficiency virus (HIV) coinfection, hepatitis B virus (HBV) coinfection, and alcohol consumption. The rates of chronicity can also vary depending on the source of infection and size of inoculum (virus persistence has been associated with a large inoculum like with post-transfusion hepatitis), the immune status of the host (patients with agammaglobulinemia, or recipients of organ transplants are known to influence the disease progression), and, probably, race (higher rates of chronicity have been found in African Americans in comparison to white populations in the United States) [1, 6]. A recent report claims to have found an association between genotype 3 infection and spontaneous recovery [92]. Besides, clinical course and alanine aminotransferase (ALT) profile during acute phase of

HCV infection has also been associated with the disease outcome - patients with symptoms and jaundice, and the higher ALT peak, as well as the monophasic pattern of ALT profile have been shown to predict recovery [1, 4, 6, 10].

DIAGNOSIS OF ACUTE HCV INFECTION

Acute HCV infection is a rare diagnosis, because most patients with a new HCV infection do not experience clinical symptoms and never come to clinical attention. Only approximately one quarter of acute cases results in jaundice that might be preceded and accompanied by malaise, anorexia, nausea and pain in the right upper abdomen [1, 2]. As slight fatigue may be the only manifestation of the disease, physicians should be aware of the potential sources of infection and screen patients at risk for seroconversion from a past negative to a positive anti-HCV (antibodies to HCV) test [10, 90]. Although in the cases thought to have been at high risk or exposed to the virus, HCV RNA testing could be the choice to establish acute HCV infection [1, 2, 15]. This applies particularly in the case of needle stick accidents of healthcare workers, where HCV RNA is detectable weeks prior to the appearance of anti-HCV [13]. HCV RNA testing can also be used to screen for HCV infection in persons with negative HCV ELISA (enzyme-linked immunosorbent assay) results who are known to have conditions associated with diminished antibody production, such as HIV and hemodialysis [1]. The diagnosis of acute HCV infection is the most certain when there is a recognized exposure to HCV within the preceding 16 weeks, detectable HCV RNA by RT-PCR (reverse transcriptase polymerase chain reaction), and an acute increase in levels of ALT to >10 times the upper limit of normal, with or without increase in total bilirubin level [6]. Results of testing for anti-HCV may be positive or negative, depending on the phase of acute illness. Detection of HCV-RNA without anti-HCV is strongly indicative of acute hepatitis C, particularly when it is followed by anti-HCV seroconversion (usually 8-20 weeks after exposure), detected by the third-generation ELISA and an immunoblot-based confirmatory test. If patients are seroconverted at the time of presentation, the diagnosis of acute HCV infection may rely on documentation of prior seronegativity and/or the absence of detectable HCV-RNA [6, 10, 13-15]. A small proportion of acute HCV presentations remains antibody-negative throughout the acute phase and may recover without developing any measurable serological marker of infection. Interestingly, it has

been reported that successful viral clearance may be associated with rapid antibody loss. IgM responses specific to HCV have not proven useful in the diagnosis of acute hepatitis C, because anti-HCV IgM may be present at similar levels in both acute and chronic diseases [2, 5]. A reliable laboratory with adequate quality control procedures should be used when testing for acute HCV infection.

NATURAL COURSE OF ACUTE HCV INFECTION

Hepatitis C viral RNA typically becomes detectable and reaches high serum titres within 1-2 weeks of infection [10]. Adaptive cellular immune responses are delayed by at least 1 month, and humoral immune responses by at least 2 months in both humans and chimpanzees [1, 5, 23]. After the incubation phase, the course of acute HCV infection can be highly variable. Whereas most patients display increased ALT levels, only a few develop clinical symptoms within 5-12 weeks following exposure, and those patients have been demonstrated tend to display stronger HCV-specific immune responses with a higher likelihood of HCV clearance. The clinical syndrome, if present, lasts from 2 to 12 weeks [2, 3, 11, 14]. Severe liver function impairment or failure are extremely rare events in the absence of hepatotoxic co-factors in acute HCV infection [11]. After the first weeks of infection, viral replication rate slows and serum HCV RNA titres reach a plateau phase [71]. When serum ALT levels peak, approximately 8-12 weeks after exposure, HCV RNA titres decline. Antibodies to HCV might become detectable around this time, later or not at all, and they do not indicate the outcome of infection [16]. Typically, ALT and HCV RNA levels may peak more than once across a very broad range during acute phase, suggesting a complex pattern of virus-host interactions and the virus attempts to adapt to emerging host immune responses [5, 10, 11, 16, 49, 50]. ALT may return to normal levels between peaks and HCV RNA may intermittently become undetectable in the serum. In chronic HCV infection viral levels are typically very stable and do not vary by more than a log in an individual patient over time. It has been described that HCV viremia may recur after a period of up to 4-5 months of undetectable HCV RNA in the blood [16]. Hence, HCV may persist in the liver and/or extrahepatic sites for months after falling below the lower limit of detection in the blood. It is therefore important not to rely on a single negative PCR result and/or normal ALT during the late phase of acute HCV to avoid the false impression that the pa-

tient has recovered while instead he/she has developed persistent infection [5, 10]. Prolonged follow-up with repeated testing for at least 12 month after diagnosis is necessary to prove that the infection has resolved [11]. Acute hepatitis C is considered to run a course of approximately 6 months, a period, which appears to be the maximal length of time during which spontaneous recovery is still possible. Typically, self-limited disease occurs within the first 3 to 4 months of infection, although very rare cases of late clearance have been observed. If the infection extends beyond 6 months, the likelihood of spontaneous HCV clearance is extremely small, and in that case the term of chronic hepatitis C is applied [3, 5, 69, 70]. It has been reported that HCV-specific antibody titres decline and might disappear 10-20 years after recovery. Thus, complete HCV clearance might be achieved by at least a subgroup of patients, however it is still a matter of debate and requires further study [31].

IMMUNOLOGY OF ACUTE HCV INFECTION

INNATE IMMUNE RESPONSE

The innate immune response constitutes the first line of defense against many infectious agents. One of the first defense mechanisms that an infected host is able to mount against viral infections is the production of type I IFNs. Because of the ethical constraints on performing a liver biopsy during the acute phase of HCV infection in humans, the role of type I IFNs derives mainly from experimental studies with chimpanzees, the only animal model of HCV infection, as well as from *in vitro* models [17]. Microarray analyses of sequential chimpanzee liver biopsies during the course of HCV infection indicated that HCV induces early changes in the expression of many intrahepatic genes, including genes involved in the type I interferon response. Genes that encode IFN-regulated transcription factors are also upregulated in the acute phase of infection [5, 19, 20]. Even though HCV is highly sensitive *in vitro* to type I IFNs, it seems that HCV may develop strategies to be resistant to the antiviral effects of IFN- α and IFN- β *in vivo* [16, 40-42]. As the result – the initial production of type I IFNs only may slow, but not block viral replication.

In addition, HCV may also interfere with the function of innate effector cells, such as natural killer (NK) cells. NK and NK-T cells are the components of the innate immune system that respond within minutes or hours after infection by production IFN- γ and by

killing infected cells [21]. IFN- γ production by these cells not only has antiviral effects but also mediate the intrahepatic recruitment of inflammatory cells [22]. The absence of signs of liver inflammation in the first 4 to 6 weeks after HCV infection [19, 23, 24] suggest that the contribution of NK and/or NK-T cells in this early phase may be minimal. Such possibility is supported by recent data showing that the HCV envelope protein E2 can inhibit NK cell function directly by interacting with CD81 molecule expressed on the surface of NK cells [16].

Signals delivered by the innate immune system (type I IFN production, interactions with NK cells) lead to the proper maturation of dendritic cells (DC), which are critical for triggering the antigen-specific immune response [16]. It is possible that an alteration of the DC function and/or maturation during primary HCV infection can contribute to the delayed appearance of HCV specific T cells after infection. NK cell activation contributes to DC maturation [25]. The inhibitory effect of the HCV envelope protein on NK cell function may influence indirectly the function of DCs to trigger the adaptive response. Furthermore, alteration of DCs may be related directly to the effect of HCV proteins [26].

The coexistence of early HCV replication with the absence of signs of liver inflammation is not only indicative of the noncytotoxic nature of HCV, but also suggests pathogenic contribution of the early innate immune response, which may favor persistent HCV infection.

HUMORAL IMMUNE RESPONSE

HCV-specific antibodies are not detected for weeks to months after infection. The time to seroconversion is highly variable, ranging from 4 to more than 20 weeks after exposure [5, 10]. During acute HCV infection antibodies against the core protein are detected earlier than those against the envelope or NS proteins [2, 27, 28]. Typically, in the early stages of infection, the patient has low level ELISA positivity that increase as infection continues. Unlike HBV infection, a role for antibodies in protection against natural HCV infection has been difficult to prove. Emergence of HCV-specific antibodies does not correlate temporally with the disease outcome. Indeed, although usually all immunocompetent persons develop multiple antibodies to a range of HCV antigens, most infections persist [2, 28, 29]. A few patients may resolve without developing any measurable serological marker of the infection [5, 16]. Furthermore, viral recovery also has

been described in HCV-infected agammaglobulinemic patients, providing evidence that control of HCV can occur independently of antibodies [29, 30]. More commonly, antibody levels continuously decrease after the virus has been cleared, and might be undetectable decades after spontaneous HCV clearance in some patients [5, 31].

Besides, antibody responses do not appear to “mature” during the course of acute HCV infection, and are restricted to the IgG1 subclass [16, 32]. A diverse immunoglobulin subclass repertoire is probably necessary to control viral infection. Therefore, the narrow switching found in HCV infection may contribute to viral persistence [27]. Also, Chen et al. reported, that compared to other hepatotropic viruses, HCV antibody responses have relatively low titres [32].

Neutralizing antibody responses often provide the first line of adaptive humoral defense against infection by limiting virus spread. However, the existence of neutralizing antibodies to HCV and their role to the outcome of infection are still controversial. Antibodies specific for the HCV envelope glycoproteins (E1 and E2) have been shown to neutralize *in vivo* infectivity of HCV in chimpanzees, and to modulate HCV RNA levels in vaccinated and rechallenged chimpanzees [34, 35]. It was also demonstrated that an early antibody response to the HVR-1 of the HCV E2 protein is associated with a self-limited course of hepatitis [36], and that initial quasispecies distribution of HVR-1 is associated with HCV persistence [37]. However, recovery from hepatitis C may occur in the absence of any antibody response to the envelope proteins [93], and HCV persistence has been observed in the absence of sequence changes in the envelope proteins and specifically the HVR-1 region in the chimpanzee model [24, 93]. Anti-HCV presence in the chronically infected host, and re-infection of HCV in once-recovered chimpanzees also argue against an efficient virus neutralizing activity *in vivo* [28, 33]. The recent development of tissue-culture-based assays has allowed the assessment of humoral immune responses against conformational epitopes, however further characterization of neutralizing responses during acute HCV infection is crucial to understand the role of humoral immunity in HCV control [5, 16, 27, 38, 39].

CELLULAR IMMUNE RESPONSE

Effective clearance of acute viral infection typically requires the coordinated function of multiple arms of the immune system, including the innate immune system, as well as the adaptive immune response spe-

cific to given pathogen. The cellular immune response seems to be of central importance for the outcome of acute HCV infection [2, 6, 17, 43]. CD4+ T cell responses are critical to both the generation and maintenance of antiviral immune responses, because they secrete cytokines that augment antibody production by B cells and prime CD8+ T cells specific for virus-infected cells [28, 44]. In both experimental chimpanzee and natural human infection, clearance of HCV is associated with strong, polyclonal, and sustained HCV-specific CD4+ T cell responses [31, 43, 47, 51, 52, 54, 55]. The appearance of these CD4+ T cell responses in the chimpanzees during acute HCV infection is associated with a substantial decrease in viraemia, and the accumulation of HCV-specific CD4+ T cells in the liver appears to be essential for clearance of HCV [43, 55]. In the acute phase of hepatitis C and also in long term recovery patients typically recognize a mean of 10 different CD4+ T cell epitopes, although the range might be quite broad with some patients responding up to 20 epitopes [56, 57]. The majority of immunodominant epitopes is located within non-structural proteins NS3 to NS5 [28, 47-50, 56, 57]. Additionally, IFN- γ producing T-helper 1 type CD4+ T cell responses directed against multiple HCV proteins were found to persist in most patients who experienced spontaneous resolution of HCV infection, even when measured many years after the time of first exposure to the virus [31, 50]. Persons who clear HCV infection have a more rapid and sustained induction of CD4+ T cells responses, whereas loss of HCV-specific CD4+ T cells during the initial months of infection is associated with relapse of viraemia [23, 50]. A substantial proportion of patients who eventually develop chronic hepatitis C go through a phase of transient viral control with undetectable or very low hepatitis C viraemia. During this period, strong and multi-specific CD4+ T cell responses can be measured. However, upon recrudescence of viraemia, CD4+ T cell responses rapidly wane and remain at low or undetectable levels throughout the chronic phase of the disease [49, 50]. The mechanisms leading to this down regulation of HCV specific CD4+ T cell responses are still poorly understood, but it is very likely an important contributing factor to chronic viral persistence.

Virus specific CD8+T cells are considered to be the major antiviral effector cells. They recognize viral peptides presented by HLA (human leukocyte antigens) class I molecules on virus infected cells. Antiviral effects are mediated either by lysis of infected cells or by non-cytolytic mechanisms, where viral replication is suppressed by secretion of cytokines like IFN- γ or

TNF- α (tumor necrosis factor) [2, 58]. The importance of an HCV-specific CD8+ T cell response in viral clearance has been demonstrated in chimpanzee and human studies [23, 29, 43, 59]. An early, vigorous intrahepatic CTL response directed against multiple protein targets was found in resolved chimpanzees, whereas those that went on to develop chronic infection had a more narrowly focused response during acute infection. HCV-specific IFN- γ -secreting CD8+ T cells are abundant in chimpanzees that recovered, compared with levels in chimpanzees with chronic infection [29, 53, 60]. In humans the onset of viral load reduction during acute HCV infection is also closely associated with the development of an HCV specific CD8+ T cell response [23]. Similar to the CD4+ T cell response, stable CD8+ T cell responses are maintained in patients with resolving HCV infection, whereas both strength and breadth of CD8+ T cells decline in chronically infected individuals. Important factor that may explain the failure of HCV CD8+ T cell responses to eliminate the virus may be functional impairment. Published observations have suggested that most of HCV specific CD8+ T cells have impaired production of IFN- γ , low perforin content and defective capacity for expansion or lytic activity [63-65]. These functional defects are transient in patients who clear the virus spontaneously [59], while the impairment of proliferative, cytokine and cytotoxic effector functions persist long-term in patients with chronic hepatitis C infection [72]. Furthermore, the importance of memory CD8+ T cells in control of HCV infection was demonstrated in experimental HCV infection in chimpanzees [61]. Following depletion of CD8+ T cells the animals were unable to eliminate the virus and only when CD8+ T cells recovered, a decline and finally elimination of HCV was observed. The persistence of HCV-specific memory CD8+ T cells suggests that virus-specific CD4+ T cells similarly persist [2]. Their importance in maintaining an effective CD8+ T cell response was reported by Grakoui et al. [62]. Interestingly, it was also reported that chronic HCV infection develops and persists in major infected persons despite the presence of HCV-specific CD4+ and CD8+ T cell responses in the peripheral blood and liver, suggesting that these responses are, for the most part, ineffective [73-79]. It is likely that HCV has developed a number of means to evade host defenses, although most literature has focused on the role that quasispecies variability plays as a mechanism of escaping immune defenses [9, 80-82]. However, several other potential mechanisms have been proposed to counteract the adaptive immune response and to

mediate viral persistence. These include suppression of host immune responses by HCV proteins through interference with T cell function [83], suboptimal IL-2 production and incomplete maturation and differentiation status of HCV-specific T cells [5], abnormal dendritic cell function [18, 84], host genetic factors, such as polymorphism in cytokine gene promoters or chemokine-receptor genes, and possible CD4+CD25+ T-regulatory cells [16], among others.

TREATMENT OF ACUTE HCV INFECTION

The high propensity of acute hepatitis C to become chronic provides a strong rationale for antiviral therapy. Several published studies have clearly demonstrated the beneficial effect of the interferon (IFN) treatment in the eradication of HCV during acute infection and preventing the progression to chronic hepatitis [12, 85, 86, 88]. Besides, those who successfully eradicated the virus with treatment appear to remain virus-free in the long term [85].

However, as yet, there is no standard therapy for acute hepatitis C, principally due to the difficulty in organizing large randomized trials, which are necessary to produce guidelines for clinical management and treatment. Most of the reported studies have been small in size, uncontrolled, and highly heterogeneous in terms of patient features and study design. For these reasons it is not yet clear which patients should be treated, when therapy should be started and what regimen is optimal.

In theory, suppression of HCV replication by IFN therapy during the early phase of acute hepatitis may favor the patient's immune system to clear the virus and prevent the development of chronic infection. According to this possibility, immediate initiation of therapy for acute hepatitis C is desirable before immunologic mechanisms for persistent infection are established. In fact, reported rates of spontaneous HCV clearance are variable, in the range of 10-60% depending on the route of transmission, underlying illness, age and other virus and host factors [5]. Thus, the major disadvantage of the immediate treatment strategy is that exposing patients who spontaneously clear the virus to unnecessary treatment.

Recently, Ogata and colleagues have found that the rate of sustained clearance of HCV was significantly high when IFN therapy was initiated within 24 weeks compared to later than 24 weeks [87]. Furthermore, as long as the therapy was initiated within 6 months, the earlier timing of therapy was not associated with the improved rate of HCV clearance. The results suggest

that immediate therapy at the onset of acute hepatitis is not necessary and the initiation of therapy could be delayed after a period of careful waiting for spontaneous clearance of HCV, avoiding of an useless, potentially harmful and costly treatment of patients with a self-limiting disease. Another randomized controlled trial has also demonstrated high SVR (sustained virological response) rates (87-100%), when IFN- α therapy was started 8 weeks after the onset of acute hepatitis C. Unfortunately, SVR fell to 40-53% if treatment was delayed by 1 year [89]. Meanwhile, a recent meta-analysis showed that delaying therapy by 8-12 weeks after the onset of acute hepatitis does not compromise the rate of HCV clearance [90]. The spontaneous clearance of HCV is likely to occur within 4-12 weeks of infection [12, 85]. Observations imply that immediate therapy of acute HCV infection is too early and waiting for more than 24 weeks is too late. Thus, optimal timing for the IFN treatment may end up within a period of 8-24 weeks after the onset of acute hepatitis [4, 6, 11, 87, 89].

Since there are no reliable predictors to identify which patients are unlikely to clear the virus spontaneously, thus, controversy also remains on which patients should be treated. If the likelihood of chronicity in individual patients could be predicted, therapy could be started with no delay in high risk patients. Symptomatic onset of the disease, younger age, and female sex were significantly associated with a self-limited course of HCV infection [10, 11, 87]. HCV genotype 3 has been also associated with spontaneous clearance of infection. In addition, genotypes 2 and 3 display higher SVR after the treatment of chronic infection [10, 92]. Furthermore, patients with the fluctuation of ALT levels are unlikely to clear the virus spontaneously [87]. From these observations, asymptomatic, non-icteric patients with the fluctuation of ALT levels and those, infected with genotypes other than 2 or 3 might be one of the high risk groups for the development of chronic infection and thus therapy should be initiated without delay.

Another important issue is what regimen of therapy should be used. Some authors have suggested that an initial induction period with high dose of standard IFN (e.g., 5-10 MU daily for the first month) results in higher response rates (up to 98%) compared to conventional dosing with IFN three times per week [2, 5, 88, 90]. This rate of recovery is higher than the rate of spontaneous clearance and also than the rate of response to the best of treatment available for chronic hepatitis C, although the reasons for the dramatic difference in the sensitivity to treatment of acute and

chronic infection are unknown. Presently, several studies indicate that PegIFN (pegylated interferon) monotherapy is equally effective and achieves SVR around 95% [10, 85, 86, 91]. The convenience of administering PegIFN with a weekly injection should enhance compliance. Combination therapy of ribavirin and IFN or PegIFN, which is now the standard regimen for chronic hepatitis, may not have additive value over mono-therapy in acute hepatitis since the rate of sustained clearance of HCV is already high with mono-therapy [5, 90].

The duration of therapy for acutely infected HCV patients has varied between studies. It is likely, that 24 weeks of therapy may be adequate [5, 92]. Some studies achieved high response rates using a 6 months course, while other authors reported a SVR rate of 100% using daily induction dosing with IFN for 12 weeks, followed by standard dosing for 40 weeks [91]. To the contrary, data from a recent Japanese study [89] demonstrated that even shorter course of daily injection with 6MU of standard IFN- α for only 4 weeks is effective in 87% of patients. Due to the heterogeneity of the data and the results, the optimal treatment dosage and duration in this population has not been entirely clarified.

Hence, although significant strides have been made, further studies of adequate size and designs are urgently needed in this field to better define the optimal guidelines and regimens for the treatment of acute hepatitis C.

REFERENCES

1. Mandell GL, Bennett JE, Dolin R. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 6th ed. USA; 2005.
2. Orland JR, Wright TL, Cooper S. Acute hepatitis C. *Hepatology*. 2001 Feb; 33(2):321-7.
3. Busch MP, Shafer KA. Acute-phase hepatitis C virus infection: implications for research, diagnosis, and treatment. *Clin Infect Dis*. 2005 Apr 1;40(7):959-6
4. Thomson BJ, Finch RG. Hepatitis C virus infection. *Clin Microbiol Infect*. 2005 Feb;11(2):86-94.
5. Heller T, Rehermann B. Acute hepatitis C: a multifaceted disease. *Semin Liver Dis*. 2005 Feb;25(1):7-17.
6. Chung RT. Acute hepatitis C virus infection. *Clin Infect Dis*. 2005 Jul 1;41 Suppl 1:S14-7.
7. Bowen DG, Walker CM. The origin of quasispecies: cause or consequence of chronic hepatitis C viral infection? *J Hepatol*. 2005 Mar;42(3):408-17.
8. Penin F, Dubuisson J, Rey FA, Moradpour D, Pawlotsky JM. Structural biology of hepatitis C virus. *Hepatology*. 2004 Jan;39(1):5-19.
9. Farci P, Shimoda A, Coiana A, et al. The outcome of

- acute hepatitis C predicted by the evolution of the viral quasispecies. *Science*. 2000 Apr 14; 288(5464):339-44.
10. Mondelli MU, Cerino A, Cividini A. Acute hepatitis C: diagnosis and management. *J Hepatol*. 2005;42 Suppl(1): S108-14.
 11. Alberti A, Benvegno L. Management of hepatitis C. *J Hepatol*. 2003;38 Suppl 1:S104-18.
 12. Alberti A, Boccato S, Vario A, Benvegno L. Therapy of acute hepatitis C. *Hepatology*. 2002 Nov;36(5 Suppl 1): S195-200.
 13. Moller JM, Krarup HB. Diagnosis of acute hepatitis C: anti-HCV or HCV-RNA? *Scand J Gastroenterol*. 2003 May;38(5):556-8.
 14. Wawrzynowicz-Syczewska M, Kubicka J, Lewandowski Z, Boron-Kaczmarek A, Radkowski M. Natural history of acute symptomatic hepatitis type C. *Infection*. 2004 Jun; 32(3):138-43.
 15. Sarrazin Ch. Diagnosis of hepatitis C: update 2004. *J Gastroenterol Hepatol*. 2004; 19, S88-S93.
 16. Rehmann B, Nascimbeni M. Immunology of hepatitis B virus and hepatitis C virus infection. *Nat Rev Immunol*. 2005 Mar;5(3):215-29.
 17. Bertolotti A, Ferrari C. Kinetics of the immune response during HBV and HCV infection. *Hepatology*. 2003 Jul;38(1):4-13.
 18. Pachiadakis I, Pollara G, Chain BM, Naoumov NV. Is hepatitis C virus infection of dendritic cells a mechanism facilitating viral persistence? *Lancet Infect Dis*. 2005 May;5(5):296-304.
 19. Bigger CB, Brasky KM, Lanford RE. DNA microarray analysis of chimpanzee liver during acute resolving hepatitis C virus infection. *J Virol*. 2001 Aug;75(15):7059-66.
 20. Su AI, Pezacki JP, Wodicka L, et al. Genomic analysis of the host response to hepatitis C virus infection. *Proc Natl Acad Sci U S A*. 2002 Nov 26;99(24):15669-74.
 21. Biron CA, Brossay L. NK cells and NKT cells in innate defense against viral infections. *Curr Opin Immunol*. 2001 Aug;13(4):458-64.
 22. Liu ZX, Govindarajan S, Okamoto S, Dennert G. NK cells cause liver injury and facilitate the induction of T cell-mediated immunity to a viral liver infection. *J Immunol*. 2000 Jun 15;164(12):6480-6.
 23. Thimme R, Oldach D, Chang KM, Steiger C, Ray SC, Chisari FV. Determinants of viral clearance and persistence during acute hepatitis C virus infection. *J Exp Med*. 2001 Nov 19;194(10):1395-406.
 24. Major ME, Mihalik K, Fernandez J, et al Long-term follow-up of chimpanzees inoculated with the first infectious clone for hepatitis C virus. *J Virol*. 1999 Apr;73(4):3317-25.
 25. Piccioli D, Sbrana S, Melandri E, Valiante NM. Contact-dependent stimulation and inhibition of dendritic cells by natural killer cells. *J Exp Med*. 2002 Feb 4;195(3):335-41.
 26. Sarobe P, Lasarte JJ, Casares N, et al. Abnormal priming of CD4(+) T cells by dendritic cells expressing hepatitis C virus core and E1 proteins. *J Virol*. 2002 May;76(10):5062-70.
 27. Netski DM, Mosbruger T, Depla E, et al. Humoral immune response in acute hepatitis C virus infection. *Clin Infect Dis*. 2005 Sep 1;41(5):667-75. Epub 2005 Jul 22.
 28. Diepolder HM, Zachoval R, Hoffmann RM, Jung MC, Gerlach T, Pape GR. The role of hepatitis C virus specific CD4+ T lymphocytes in acute and chronic hepatitis C. *J Mol Med*. 1996 Oct;74(10):583-8.
 29. Cooper S, Erickson AL, Adams EJ, et al. Analysis of a successful immune response against hepatitis C virus. *Immunity*. 1999 Apr;10(4):439-49.
 30. Post JJ, Pan Y, Freeman AJ, et al. Hepatitis C Incidence and Transmission in Prisons Study (HITS) Group. Clearance of hepatitis C viremia associated with cellular immunity in the absence of seroconversion in the hepatitis C incidence and transmission in prisons study cohort. *J Infect Dis*. 2004 May 15;189(10):1846-55.
 31. Takaki A, Wiese M, Maertens G, et al. Cellular immune responses persist and humoral responses decrease two decades after recovery from a single-source outbreak of hepatitis C. *Nat Med*. 2000 May;6(5):578-82.
 32. Chen M, Sallberg M, Sonnerborg A, et al. Limited humoral immunity in hepatitis C virus infection. *Gastroenterology*. 1999 Jan;116(1):135-43.
 33. Lavillette D, Morice Y, Germanidis G, et al. Human serum facilitates hepatitis C virus infection, and neutralizing responses inversely correlate with viral replication kinetics at the acute phase of hepatitis C virus infection. *J Virol*. 2005 May;79(10):6023-34.
 34. Farci P, Alter HJ, Wong DC, et al. Prevention of hepatitis C virus infection in chimpanzees after antibody-mediated in vitro neutralization. *Proc Natl Acad Sci U S A*. 1994 Aug 2;91(16):7792-6.
 35. Forns X, Payette PJ, Ma X, et al. Vaccination of chimpanzees with plasmid DNA encoding the hepatitis C virus (HCV) envelope E2 protein modified the infection after challenge with homologous monoclonal HCV. *Hepatology*. 2000 Sep;32(3):618-25.
 36. Zibert A, Meisel H, Kraas W, Schulz A, Jung G, Roggen-dorf M. Early antibody response against hypervariable region 1 is associated with acute self-limiting infections of hepatitis C virus. *Hepatology*. 1997 May;25(5):1245-9.
 37. Ray SC, Wang YM, Laeyendecker O, Ticehurst JR, Villano SA, Thomas DL. Acute hepatitis C virus structural gene sequences as predictors of persistent viremia: hypervariable region 1 as a decoy. *J Virol*. 1999 Apr;73(4):2938-46.
 38. Baumert TF, Wellnitz S, Aono S et al. Antibodies against hepatitis C virus-like particles and viral clearance in acute and chronic hepatitis C. *Hepatology*. 2000 Sep;32(3):610-7.
 39. Logvinoff C, Major ME, Oldach D, et al. Neutralizing antibody response during acute and chronic hepatitis C virus infection. *Proc Natl Acad Sci U S A*. 2004 Jul 6;101(27):10149-54.
 40. Foy E, Li K, Wang C, et al. Regulation of interferon regulatory factor-3 by the hepatitis C virus serine protease. *Science*. 2003 May 16;300(5622):1145-8.
 41. Taylor DR, Shi ST, Romano PR, Barber GN, Lai MM. Inhibition of the interferon-inducible protein kinase PKR

- by HCV E2 protein. *Science*. 1999 Jul 2;285(5424):107-10.
42. Gale MJ Jr, Korth MJ, Katze MG. Repression of the PKR protein kinase by the hepatitis C virus NS5A protein: a potential mechanism of interferon resistance. *Clin Diagn Virol*. 1998 Jul 15;10(2-3):157-62.
 43. Thimme R, Bukh J, Spangenberg HC, et al. Viral and immunological determinants of hepatitis C virus clearance, persistence, and disease. *Proc Natl Acad Sci U S A*. 2002 Nov 26;99(24):15661-8.
 44. Cramp ME, Carucci P, Rossol S, et al. Hepatitis C virus (HCV) specific immune responses in anti-HCV positive patients without hepatitis C viraemia. *Gut*. 1999 Mar;44(3):424-9.
 45. Naoumov NV. Hepatitis C virus-specific CD4(+) T cells: do they help or damage? *Gastroenterology*. 1999 Oct;117(4):1012-4.
 46. Tsai SL, Liaw YF, Chen MH, Huang CY, Kuo GC. Detection of type 2-like T-helper cells in hepatitis C virus infection: implications for hepatitis C virus chronicity. *Hepatology*. 1997 Feb;25(2):449-58.
 47. Missale G, Bertoni R, Lamonaca V, et al. Different clinical behaviors of acute hepatitis C virus infection are associated with different vigor of the anti-viral cell-mediated immune response. *J Clin Invest*. 1996 Aug 1;98(3):706-14.
 48. Wertheimer AM, Miner C, Lewinsohn DM, Sasaki AW, Kaufman E, Rosen HR. Novel CD4+ and CD8+ T-cell determinants within the NS3 protein in subjects with spontaneously resolved HCV infection. *Hepatology*. 2003 Mar;37(3):577-89.
 49. Rahman F, Heller T, Sobao Y, et al. Effects of antiviral therapy on the cellular immune response in acute hepatitis C. *Hepatology*. 2004 Jul;40(1):87-97.
 50. Gerlach JT, Diepolder HM, Jung MC, et al. Recurrence of hepatitis C virus after loss of virus-specific CD4(+) T-cell response in acute hepatitis C. *Gastroenterology*. 1999 Oct;117(4):933-41.
 51. Lauer GM, Barnes E, Lucas M, et al. High resolution analysis of cellular immune responses in resolved and persistent hepatitis C virus infection. *Gastroenterology*. 2004 Sep;127(3):924-36.
 52. Tsai SL, Liaw YF, Chen MH, Huang CY, Kuo GC. Detection of type 2-like T-helper cells in hepatitis C virus infection: implications for hepatitis C virus chronicity. *Hepatology*. 1997 Feb;25(2):449-58.
 53. Shata MT, Anthony DD, Carlson NL, et al. Characterization of the immune response against hepatitis C infection in recovered, and chronically infected chimpanzees. *J Viral Hepat*. 2002 Nov;9(6):400-10.
 54. Day CL, Lauer GM, Robbins GK, et al. Broad specificity of virus-specific CD4+ T-helper-cell responses in resolved hepatitis C virus infection. *J Virol*. 2002 Dec;76(24):12584-95.
 55. Woollard DJ, Grakoui A, Shoukry NH, Murthy KK, Campbell KJ, Walker CM. Characterization of HCV-specific Patr class II restricted CD4+ T cell responses in an acutely infected chimpanzee. *Hepatology*. 2003 Nov;38(5):1297-306.
 56. Schulze zur Wiesch J, Lauer GM, Day CL, et al. Broad repertoire of the CD4+ Th cell response in spontaneously controlled hepatitis C virus infection includes dominant and highly promiscuous epitopes. *J Immunol*. 2005 Sep 15;175(6):3603-13.
 57. Gerlach JT, Ulsenheimer A, Gruner NH, et al. Minimal T-cell-stimulatory sequences and spectrum of HLA restriction of immunodominant CD4+ T-cell epitopes within hepatitis C virus NS3 and NS4 proteins. *J Virol*. 2005 Oct;79(19):12425-33.
 58. Guidotti LG, Ando K, Hobbs MV, et al. Cytotoxic T lymphocytes inhibit hepatitis B virus gene expression by a noncytolytic mechanism in transgenic mice. *Proc Natl Acad Sci U S A*. 1994 Apr 26;91(9):3764-8.
 59. Lechner F, Wong DK, Dunbar PR, et al. Analysis of successful immune responses in persons infected with hepatitis C virus. *J Exp Med*. 2000 May 1;191(9):1499-512.
 60. Nascimbeni M, Mizukoshi E, Bosmann M, et al. Kinetics of CD4+ and CD8+ memory T-cell responses during hepatitis C virus rechallenge of previously recovered chimpanzees. *J Virol*. 2003 Apr;77(8):4781-93.
 61. Shoukry NH, Grakoui A, Houghton M, et al. Memory CD8+ T cells are required for protection from persistent hepatitis C virus infection. *J Exp Med*. 2003 Jun 16;197(12):1645-55.
 62. Grakoui A, Shoukry NH, Woollard DJ, et al. HCV persistence and immune evasion in the absence of memory T cell help. *Science*. 2003 Oct 24;302(5645):659-62.
 63. Lechner F, Gruener NH, Urbani S, et al. CD8+ T lymphocyte responses are induced during acute hepatitis C virus infection but are not sustained. *Eur J Immunol*. 2000 Sep;30(9):2479-87.
 64. Gruener NH, Lechner F, Jung MC, et al. Sustained dysfunction of antiviral CD8+ T lymphocytes after infection with hepatitis C virus. *J Virol*. 2001 Jun;75(12):5550-8.
 65. Urbani S, Boni C, Missale G, et al. Virus-specific CD8+ lymphocytes share the same effector-memory phenotype but exhibit functional differences in acute hepatitis B and C. *J Virol*. 2002 Dec;76(24):12423-34.
 66. Noursbaum JB, Pol S, Nalpas B, Landais P, Berthelot P, Brechot C. Hepatitis C virus type 1b (II) infection in France and Italy. Collaborative Study Group. *Ann Intern Med*. 1995 Feb 1;122(3):161-8.
 67. Kim WR. The burden of hepatitis C in the United States. *Hepatology*. 2002 Nov;36(5 Suppl 1):S30-4.
 68. National Institutes of Health. National Institutes of Health Consensus Development Conference Statement: Management of hepatitis C: 2002--June 10-12, 2002. *Hepatology*. 2002 Nov;36(5 Suppl 1):S3-20.
 69. Gerlach JT, Diepolder HM, Zachoval R, et al. Acute hepatitis C: high rate of both spontaneous and treatment-induced viral clearance. *Gastroenterology*. 2003 Jul;125(1):80-8.
 70. Hofer H, Watkins-Riedel T, Janata O, et al. Spontaneous viral clearance in patients with acute hepatitis C can be predicted by repeated measurements of serum viral load. *Hepatology*. 2003 Jan;37(1):60-4.
 71. Major ME, Dahari H, Mihalik K, et al. Hepatitis C virus kinetics and host responses associated with disease and

- outcome of infection in chimpanzees. *Hepatology*. 2004 Jun;39(6):1709-20.
72. Wedemeyer H, He XS, Nascimbeni M, et al. Impaired effector function of hepatitis C virus-specific CD8+ T cells in chronic hepatitis C virus infection. *J Immunol*. 2002 Sep 15;169(6):3447-58.
 73. Koziel MJ, Dudley D, Wong JT, et al. Intrahepatic cytotoxic T lymphocytes specific for hepatitis C virus in persons with chronic hepatitis. *J Immunol*. 1992 Nov 15;149(10):3339-44.
 74. Koziel MJ, Dudley D, Afdhal N, et al. HLA class I-restricted cytotoxic T lymphocytes specific for hepatitis C virus. Identification of multiple epitopes and characterization of patterns of cytokine release. *J Clin Invest*. 1995 Nov;96(5):2311-21.
 75. He XS, Rehermann B, Lopez-Labrador FX, et al. Quantitative analysis of hepatitis C virus-specific CD8(+) T cells in peripheral blood and liver using peptide-MHC tetramers. *Proc Natl Acad Sci U S A*. 1999 May 11;96(10):5692-7.
 76. Schirren CA, Jung MC, Gerlach JT, et al. Liver-derived hepatitis C virus (HCV)-specific CD4(+) T cells recognize multiple HCV epitopes and produce interferon gamma. *Hepatology*. 2000 Sep;32(3):597-603.
 77. Penna A, Missale G, Lamonaca V, et al. Intrahepatic and circulating HLA class II-restricted, hepatitis C virus-specific T cells: functional characterization in patients with chronic hepatitis C. *Hepatology*. 2002 May;35(5):1225-36.
 78. Rico MA, Quiroga JA, Subira D, et al. Features of the CD4+ T-cell response in liver and peripheral blood of hepatitis C virus-infected patients with persistently normal and abnormal alanine aminotransferase levels. *J Hepatol*. 2002 Mar;36(3):408-16.
 79. Grabowska AM, Lechner F, Klenerman P, et al. Direct ex vivo comparison of the breadth and specificity of the T cells in the liver and peripheral blood of patients with chronic HCV infection. *Eur J Immunol*. 2001 Aug;31(8):2388-94.
 80. Klenerman P, Lucas M, Barnes E, Harcourt G. Immunity to hepatitis C virus: stunned but not defeated. *Microbes Infect*. 2002 Jan;4(1):57-65.
 81. Weiner AJ, Geysen HM, Christopherson C, et al. Evidence for immune selection of hepatitis C virus (HCV) putative envelope glycoprotein variants: potential role in chronic HCV infections. *Proc Natl Acad Sci U S A*. 1992 Apr 15;89(8):3468-72.
 82. Wang H, Eckels DD. Mutations in immunodominant T cell epitopes derived from the nonstructural 3 protein of hepatitis C virus have the potential for generating escape variants that may have important consequences for T cell recognition. *J Immunol*. 1999 Apr 1;162(7):4177-83.
 83. Large MK, Kittlesen DJ, Hahn YS. Suppression of host immune response by the core protein of hepatitis C virus: possible implications for hepatitis C virus persistence. *J Immunol*. 1999 Jan 15;162(2):931-8.
 84. Bain C, Fatmi A, Zoulim F, Zarski JP, Trepo C, Inchauspe G. Impaired allostimulatory function of dendritic cells in chronic hepatitis C infection. *Gastroenterology*. 2001 Feb;120(2):512-24.
 85. Santantonio T, Fasano M, Sinisi E, et al. Efficacy of a 24-week course of PEG-interferon alpha-2b monotherapy in patients with acute hepatitis C after failure of spontaneous clearance. *J Hepatol*. 2005 Mar;42(3):329-33.
 86. Scotto G, Palumbo E, Fazio V, Cibelli DC, Saracino A, Angarano G. Peginterferon alfa-2b treatment for patients affected by acute hepatitis C: presentation of six case reports. *Infection*. 2005 Feb;33(1):30-2.
 87. Ogata K, Ide T, Kumashiro R, et al. Timing of interferon therapy and sources of infection in patients with acute hepatitis C. *Hepatol Res*. 2005 Dec 13;
 88. Jaeckel E, Cornberg M, Wedemeyer H, et al. Treatment of acute hepatitis C with interferon alfa-2b. *N Engl J Med*. 2001 Nov 15;345(20):1452-7.
 89. Nomura H, Sou S, Tanimoto H, et al. Short-term interferon-alfa therapy for acute hepatitis C: a randomized controlled trial. *Hepatology*. 2004 May;39(5):1213-9.
 90. Licata A, Di Bona D, Schepis F, Shahied L, Craxi A, Camma C. When and how to treat acute hepatitis C? *J Hepatol*. 2003 Dec;39(6):1056-62.
 91. Zekry A, Patel K, McHutchison JG. Treatment of acute hepatitis C infection: more pieces of the puzzle? *J Hepatol*. 2005 Mar;42(3):293-6.
 92. Dhiman RK, Chawla Y. Acute viral hepatitis C should be treated. *Indian J Gastroenterol*. 2005 Mar-Apr;24(2):68-71.
 93. Bassett SE, Thomas DL, Brasky KM, Lanford RE. Viral persistence, antibody to E1 and E2, and hypervariable region 1 sequence stability in hepatitis C virus-inoculated chimpanzees. *J Virol*. 1999 Feb;73(2):1118-26.
 94. Ramadori G, Meier V. Hepatitis C virus infection: 10 years after the discovery of the virus. *Eur J Gastroenterol Hepatol*. 2001 May;13(5):465-71.

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