HCV Carriers with Persistently Normal ALT Levels: not Too Much Healthy, not True Patients*

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Abstract

Approximately 30% of patients with chronic HCV infection show persistently normal alaninaminotransferase (ALT) levels. The majority of HCV carriers are females, and up to 40-50% of carriers harbor non-1 genotype, at least in western Europe. No association has been found between HCV type/viral load and the severity of liver damage. The prevalence of HCV carriers with normal liver seems to be very low (less than 20%). Liver disease is usually minimal/mild and fibrosis is generally absent or minimal, although the association of normal ALT with cirrhosis or with hepatocellular carcinoma has been reported. In all studies, liver histology was, on average, significantly less severe in subjects with persistently normal ALT than with abnormal ALT. Although the majority of data seem to show that HCV carriers with normal ALT have mild and stable disease, with a favourable prognosis, several studies reported a significant progression of fibrosis in approximately 20-30% of the patients with ALT normality, and the development of hepatocellular carcinoma in some cases has been described, despite persistent ALT normality. Sudden worsening of disease with ALT increase and histological deterioration has been described after up to 15 years of follow-up.

Key words

Aminotransferases - HCV infection - prognosis - therapy

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Rezumat

Aproximativ 75% dintre pacienții cu infecție cronică cu VHC prezintă transaminaze (ALT) persistent normale. Majoritatea purtătorilor de VHC sunt femei, şi până la 40-50% dintre purtători au genotipul non-1, cel puțin în vestul Europei. Nu s-a constatat nici o asociere între tipul VHC/încărcătura virală şi severitatea leziunilor hepatice. Prevalența purtătorilor de VHC cu ficat normal pare să fie foarte redusă (sub 20%). Boala hepatică este de obicei minimă/uşoară şi fibroza este în general absentă sau minimă, deşi s-au comunicat şi cazuri de asociere a ALT normale cu ciroza sau cancerul hepatocelular. In toate studiile, histologia a fost, în medie, semnificativ mai puțin severă la subiecții cu transaminaze persistent normale decât la cei cu ALT crescute. Deşi cele mai multe date par să indice că pacienții purtători de virus C cu transaminaze normale au boală uşoară şi stabilă, şi prognostic favorabil, unele studii raportează o progresiune semnificativă a fibrozei la aproximativ 20-30% din pacienții, şi a fost descrisă dezvoltarea cancerului hepatocelular la unele cazuri, în ciuda persistenței ALT normale. Agravarea bruscă a bolii cu creşterea ALT şi deteriorarea histologiei hepatice au fost constatate într-un interval de urmărire de până la 15 ani.

Introduction

Approximately 30% of patients with chronic HCV infection show persistently normal alanin-aminotransferase (ALT) levels (PNAL), and another 40% have minimally raised ALT values (1-3). Although formerly referred to as "healthy" or "asymptomatic" HCV carriers (4), the majority of these patients have some degree of histological liver damage (5-15), usually very mild.

Definition

According to standard definition proposed by International Consensus Conferences (3-4) the diagnosis

of HCV carrier with normal transaminase values can be made in the presence of positive anti-HCV antibodies, of a positive HCV RNA by RT-PCR and of normal alanine aminotransferase levels in at least three tests carried out at least two months apart over a period of six months. However, this is a too short observation period, as in clinical practice sudden increases in the aminotransferase levels are not uncommon, even at intervals longer than 6 months (3, 4, 11, 16, 17). Because of the characteristic fluctuating pattern of ALT values in chronic hepatitis C, only more stringent tests will make it possible to distinguish subjects with persistently normal ALT values from those in temporary biochemical remission (16, 17). Should these subgroups have different natural history and disease progression is not known (16). Liver histological activity was found to be significantly more marked among subjects with ALT flares during the follow-up than in those with PNAL (17).

Another important issue regards the range of ALT "normality" and the definition of the upper limit of the normal (ULN) for patients with CHC. The concept of "normal" ALT remains highly arbitrary (3) and the precise meaning of ULN has not been defined. Recent studies suggest that normal values currently used in clinical practice might underestimate the frequency of CLD (18-20). Indeed, in CHC ALT levels can be influenced by several other factors, such as alcohol consumption, body weight, gender, age, non-alcoholic fatty liver (21, 22).

Demographic characteristics

The majority of HCV carriers are females (5,17,23), and up to 40-50% of carriers harbor non-1 genotype, at least in western Europe (5,13,17,24, 25). No association has been found between HCV type and the severity of liver damage (5,25). Viral heterogeneity has been correlated with the severity and progression of disease in HCV carriers with PNAL with conflicting results (26,27) . Finally, no correlations have been found between the presence and the severity of histological liver damage and serum HCV RNA levels (28).

As to liver histology, the prevalence of HCV carriers with normal liver seems to be very low (less than 20%) (9,14,17,23). The majority of patients have some degree of liver damage on liver biopsy. Liver disease is usually minimal/mild and fibrosis is generally absent or minimal, although the association of normal ALT with cirrhosis (5,6,17, 29) or with HCC (13) has been reported. In all studies, liver histology was, on average, significantly less severe in subjects with PNAL than with abnormal ALT.

Natural history

The natural course of HCV infection in patients with normal ALT levels is actually not well understood, as only few studies exist (11-14). In a French study (11) no significant differences in both activity and fibrosis score were seen at the second biopsy performed after a mean follow-up of 3.5 years, while others (12) found that liver histology after 5 years of follow-up was not changed with respect to that observed at the entry to study. These data seem to show that HCV carriers with normal ALT have mild and stable disease, with a favourable prognosis. The reasons for this seemingly benign course of disease are not well understood (23, 30, 31).

However, the natural history of HCV carriers with PNAL probably is not always so benign. Several studies (13, 15) reported a significant progression of fibrosis in approximately 20-30% of the patients with well-defined ALT normality, and the development of HCC in some cases has been described, despite persistent ALT normality. Sudden worsening of disease with ALT increase and histological deterioration has been described after up to 15 years of follow-up (32).

Therapy

Should patients with CHC and normal ALT undergo antiviral treatment? It might be taken into account that interferon (IFN) treatment is associated with consistent side effects and reduced quality of life and is not inexpensive, while the risk of progression of the disease in this setting is extremely low. Further, many patients showed ALT flares during treatment. The 1997 NIH Consensus Conference (1) and the EASL Consensus Conference (2) stated that IFN treatment should not be recommended in these subjects. In the last few years, treatment of CHC has progressed from IFN monotherapy to IFN plus ribavirin combination therapy, and more recently to PEG-IFN plus ribavirin (1-3).

Using IFN plus ribavirin therapy for 24 or 48 weeks in patients with persistently normal or with minimally raised ALT levels (less than 1.3-1.5 ULN), sustained viral response rates of 25% to 50% have been reported (3). More recently, the introduction of the new combination therapy of PEG-IFN plus ribavirin allowed response rates higher than 50%, with a favourable risk-benefit ratio also in patients with benign or slow progressive disease. Although no definitive data in patients with PNAL are yet available, international studies with the new combination therapy in subjects with PNAL are under way (37). In a recent international multicenter, randomised study (37) using PEG-IFN alfa-2a (180 μg qw) plus ribavirin (800 mg qd) for 24 or 48 weeks, the overall sustained response rate was 30% in patients treated for 24 weeks and 52 % in those treated for 48 weeks. No spontaneous viral clearance was seen in the control group. In carriers with genotype 1b the response rates were 13% and 40% respectively, while in those harbouring genotype 2-3 response rate ranged from 72% (24 weeks) to 78% (48 weeks).

Given the efficacy of the new treatments, which soon became the standard of care for CHC, the 2002 NIH Consensus Development Conference suggested that the

issue of whether or not to treat subjects with PNAL should be re-evaluated, and that the issue at hand should be whether or not patients with mild disease should be treated (3).

Conclusion

ALT levels may have less importance in deciding who should be treated (3). Many other factors might influence the decision to treat, such as the age of the patient, HCV genotype, liver histology, patients motivation, symptoms, extra-hepatic manifestations, co-morbid illnesses (3, 36).

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