# Antiviral Treatment of HCV Carriers with Persistently Normal ALT Levels

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***Abstract:*** Approximately 30% of patients with chronic HCV infection show persistently normal alanine aminotransferase levels (PNAL). The prevalence of HCV carriers with normal liver seems to be very low (less than 15-20%). Liver disease is usually minimal/mild and fibrosis is generally absent or minimal, although the association of normal alanine aminotransferase (ALT) with cirrhosis or with liver cancer has been reported. In all studies, liver histology was, on average, significantly less severe in subjects with PNAL 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 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, in particular in patients harboring genotype 2. As to antiviral treatment, it has been clearly stated that it no longer seems reasonable to affirm that sustained response rates for patients with normal ALT levels are any different than those for patients with elevated ALT levels when the combination of pegylated interferon (IFN) and ribavirin is used.

The issue at hand is whether or not patients with mild disease should be treated. There are numerous other factors which impact on this decision, including genotype, histology, patients motivation, symptoms, co-morbid illness, and the age of the patient.

ALT levels may have less importance in deciding who should be treated.

## INTRODUCTION

Approximately one third of patients with chronic HCV infection show persistently normal alanine aminotransferase (ALT) levels (PNAL), and another 40% have minimally raised ALT values [1-3]. These subjects have been for long time referred to as "healthy" or "asymptomatic" HCV carriers [4], however, it is now clearly established that the majority of these patients have some degree of histological liver damage [5-15], although usually minimal or mild.

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 ALT levels in at least three tests carried out at least two months apart over a period of six months. However, in clinical practice sudden increases in the aminotransferase levels are not uncommon, even at intervals longer than 6 months [3, 4, 11, 16, 17]. 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 chronic hepatitis C (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 CHC [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].

As to liver histology, the prevalence of HCV carriers with normal liver seems to be very low (less than 20%) [9, 14, 17, 23-29]. 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 hepatocellular carcinoma (HCC) [13] has been reported. In all studies, liver histology was, on average, significantly less severe in subjects with PNAL than with abnormal ALT. No correlation exists between serum HCV RNA levels and the severity of liver damage [26-28].

The natural course of HCV infection in patients with normal ALT levels is actually not well understood, as only few studies exist [11-15]. Several authors found that that liver histology after 3-5 years of follow-up was not changed with respect to that observed at the entry to study [11-12]. 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 [14, 15] reported a significant progression of fibrosis in approxi-

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mately 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 [13]. Sudden worsening of disease with ALT increase and histological deterioration has been described after up to 15 years of follow-up, in particular in patients harboring genotype 2 [32]. This issue might have high relevance in clinical practice, as it means that it would be better to treat these patients when younger and without significant contraindications to antiviral treatment [14].

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.

The 1997 NIH Consensus Conference [1] and the EASL Consensus Conference [2] stated that IFN treatment should not be recommended in these subjects. Indeed, at this time only the results of few pilot clinical trials on interferon monotherapy or in combination with ribavirin were available [1, 3, 16], the majority of them uncontrolled. Further, the study populations were quite different, with regards to both the epidemiological setting (patients referred to a liver unit or blood donors) and to the inclusion criteria (patient age, ALT pattern , severity of the histological lesions, etc.). Finally, the administered doses did highly differ, ranging between 3 and 10 MU of interferon t.i.w. for periods from 6 to 12 months, with or without ribarivin. In these first pilot studies, the SVR was very disappointing (21%; from 0% to 41%) [1-3, 10, 22, 31-34].

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, 35-38].

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], SVR rates of 25% to 50% have been reported [3].

More recently, the introduction of the new combination therapy of pegylated (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. 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).

During the treatment, ALT levels did significantly decrease with respect to baseline levels – although already within the normal range - in patients with sustained virological response (SVR). Thus, the efficacy and safety of PEG-IFN plus RBV treatment do not differ between patients with PNAL or with elevated ALT levels: patients with HCV-1 should receive a 48-wk treatment course, whilst in those with HCV-2 or 3 therapy duration might be shorter (24 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]. 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 illness [3, 36].

When deciding to treat HCV carriers with normal ALT levels, several issues should be taken in account, and the cost to benefit ratio should be carefully evaluated. For example, physician should be alerted about the possibility that these subjects could show ALT flares during the follow-up, and that fibrosis progression accelerates after such flares. Should we wait for disease worsening and patient's ageing ? Further, many persons with PNAL must be considered as "easy-to-treat" patients (mild fibrosis, females, genotype 2 or 3): thus, in "easy-to-treat" patients should we really defer therapy, with possible subsequent risks of fibrosis progression, or occurrence of cofactors and contraindications to treatment?

However, the number of HCV patients with PNAL is huge, and the cost of treating all should be exceedingly high. Thus, antiviral treatment should be considered in those subjects at higher risk of progression, in order to avoid possible progression to cirrhosis and HCC, with possible future need of liver transplantation and of HCC treatment. The cost/benefit might be particularly favourable in two specific subsets of patients: young, easy to treat patients (showing high rate of SVR with short therapy) regardless of fibrosis score, and middle age patients with "significant" liver disease, in which the progression of the disease might occur within a few years, in particular in the presence of co-factors (steatosis, overweight, diabetes). In these latter, treatment should be only considered with fibrosis score > F2, while persons with milder degree of fibrosis (F0 to F1) might be simply followed-up.

In conclusion, among HCV carriers with PNAL, "normal" does not always mean "healthy" [36]. In the absence of contraindications, antiviral treatment with the combination therapy PEG-IFN plus ribavirin should be considered in younger patients regardless of fibrosis, in those at higher risk of progression and in subjects with high motivation to be treated, according to data from more recent literature [13, 14, 37, 39, 40]. In patients not candidates to treatment, close follow-up should be scheduled, and all factors of possible fibrosis progression should be carefully avoided (such as alcohol, steatosis, obesity, HBV, hyperlipemia, etc) [39, 40].

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