HCV carriers with normal alanine aminotransferase levels: Healthy persons or severely ill patients?
Dealing with an everyday clinical problem

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Abstract

Approximately 30% of patients with chronic HCV infection show persistently normal ALT levels. Although formerly referred to as ‘healthy’ or ‘asymptomatic’ HCV carriers, and thus historically excluded from antiviral treatment, it has now become clear that the majority of these patients have some degree of histological liver damage that may be significant in up to 20% of patients and might progress toward a more severe degree of liver fibrosis. A significant proportion of patients (≥20%) experience periods of increased serum ALT (flare) associated with enhanced disease progression. However, controversies still exist in clinical practice regarding the definition of ‘persistent’ ALT normality, the virological and histological features of these subjects, the need for liver biopsy, the role of non invasive tools for the assessment of liver fibrosis (transient hepatic elastography, fibroscan), and the natural history and optimal management of chronic hepatitis C with normal ALT. The advent of new therapeutic options (pegylated interferons plus ribavirin) has shifted treatment targets toward eradication of underlying infection, with therapy decision based on age, severity of disease and likelihood of response rather than on aminotransferase levels. This review does approach the main unresolved issues on this topic in the form of a dialog between a hepatologist and a patient with HCV infection but normal alanine aminotransferase levels, trying to give evidence-based answers to the more frequently asked questions from patients and their physicians.

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Patient: Good morning, Doctor Calm.
Doctor: Good morning, Ms Worry, how are you?
P.: Not very well Doc, I’m afraid I’m severely ill, I’m really disheartened.
D.: Calm yourself, Ms Worry, and tell me everything. Don’t be hasty!
P.: OK, Doc. Few weeks ago I did suffer from heartburn and acid reflux, so my GP said I should perform an upper digestive endoscopy. I went to the hospital, but the Gastroenterologist did prescribe several blood tests to be made before endoscopic procedure, and...
D.: And?
P.: And... I’m found to be anti-HCV positive! But my liver enzymes and blood count are normal, my GP said. I have only foggy notions! Please Doc, tell me: is my liver healthy? Do I have chronic hepatitis or cirrhosis? Will I spread the disease to my relatives? How sick will I become? Can I be cured? Is liver biopsy needed? May I have a normal life? Is liver transplantation urgently needed?
D.: Keep cool, my dear. How old are you? Did you have important diseases in the past? Do you usually drink wine or alcoholics?
P.: I’m 35 year-old, I had no important illness, I’m housewife, my husband is a teacher, we have two children. I’m teetotaler, and I never used illicit drugs. I’m 5.25 ft tall and my weight is 54 kg.
D.: First of all, I’m not sure that HCV determination before endoscopic procedures is really needed. Although the potential role of digestive endoscopy as a mode for transmission of HCV is controversial [1], several findings support the hypothesis that properly performed digestive endoscopy is not a major risk factor for the transmission [2,3], and thus a screening for hepatitis C virus infection has to be considered unjustified for persons who are scheduled for an invasive procedure, such as digestive

Abbreviations: ALT, alanine aminotransferase; HCV, hepatitis C virus; IFN, interferon; PNALT, persistently normal ALT.
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endoscopy [4]. Screening is recommended for persons who have injected illicit drugs in the recent and remote past, people infected with the HIV, hemophilic patients receiving clotting factor concentrates prior to 1987, persons who have ever been on hemodialysis, persons with unexplained abnormal aminotransferase levels, prior recipients of transfusions or organ transplants prior to 1992, children born to HCV-infected mothers, health care, emergency medical and public safety workers after a needle stick injury or mucosal exposure to HCV positive blood, current sexual partners of HCV-infected persons [5]. Thus, none of these is your case.

P.: Perhaps you are right Doc, but if I had not performed the test I would have never known to have HCV infection. Should my husband and my children be offered HCV testing?

D.: Although the prevalence of infection among household and sexual partners of HCV-infected individuals with normal ALT is very low [6], HCV prevalence in these groups was found to be significantly higher compared to controls (usually ≥3%) [4]. Thus, a negative test in the partner and children provides reassurance, making testing of relatives of benefit in clinical practice [5].

P.: OK Doc, I have understood that the probability that my households will be HCV positive is really scarce, is it correct?

D.: Yes, but there are two questions of paramount importance, Ms Worry: first, was testing for serum HCV RNA detection be made?

P.: Doc, it is so hard to understand all these steps.

D.: Please pay attention, Ms Worry. These issues are very important to know, since anti-HCV positivity with a negative test for HCV RNA may represent acute HCV infection during a period of transient clearance of HCV RNA, a false positive or negative result or, more commonly, recovery from HCV infection [5]. On the contrary, the identification of both anti-HCV and HCV RNA in a person with consistently abnormal ALT values is consistent with chronic HCV infection. The third scenario is HCV RNA positivity but with normal ALT levels [7]. So, are you HCV RNA positive or negative?

P.: HCV RNA positive, I'm afraid. There you have the results... 2.0 × 10^5 IU/mL, two hundred thousands Units of virus, I believe. I have never been good at math. What does this value mean? Is it high or low? Does the severity of liver damage depend on HCV RNA levels? Should HCV RNA determination be repeated from time to time? I believe that the prognosis of the liver disease is worst among patients with higher viral load, isn't it?

D.: Absolutely not! No correlations exist between serum HCV RNA levels and the severity of liver damage [8]. Viral load does not predict the natural history or the prognosis of HCV chronic infection, and the presence or the severity of liver damage does not depend on the entity of viral load [9]. Moreover, no correlations have been reported between ALT and HCV RNA levels [10]. Thus, the routine determination of quantitative viraemia is not indicated in clinical practice and its use should be discouraged [11].

P.: I strongly believe your words Doctor Calm, but if measurement of serum HCV RNA level is not recommended because HCV viraemia does not correlate with disease progression, what is the purpose of determining HCV RNA levels?

D.: This is a proper question, my dear. In everyday practice HCV RNA quantitation should be used to distinguish between “true” HCV carriers with normal ALT and anti-HCV positive/HCV RNA negative persons, as this latter may represent more commonly recovery from HCV infection [12]. Thus, HCV RNA testing using a quantitative assay should be routinely determined only in patients for whom antiviral treatment is being considered, in order to determine the likelihood of response and – may be – the duration of treatment [5].

P.: Doc, you said there are TWO questions of paramount importance. The first dealt with HCV RNA determination; and the second one?

D.: Right! Do you have persistently normal, transiently normal, low-normal, high-normal or abnormal alanine aminotransferase (ALT) levels?

P.: Well, four weeks ago, ALT levels were 40 IU/L, and... just a moment, please... ALT levels were 20 IU/L two years ago. I have no other data. Is it really so important to know whether ALT values were normal, half-normal, high-normal, low-normal, and so on?

D.: Yes, of course. I will try to explain to you the reasons. Approximately 30% of patients with chronic HCV infection show persistently normal ALT levels (PNALT), and another 40% have minimally raised ALT values [13–15]. Although formerly referred to as ‘healthy’ or ‘asymptomatic’ HCV carriers and thus excluded from antiviral treatment [16], it has now become clear that the majority of these patients have some degree of histological liver damage. Obviously, the definition of HCV carrier with PNALT should not be merely based upon the persistent normality of aminotransferases [11], as it implies the consistent normality of all biochemical and haematological tests, the absence of symptoms or signs of liver disease, and the normality of imaging studies.

P.: Lovely, all my blood tests are normal, and my GP said that also my liver scan goes well. Please, continue.

D.: It is known that during the course of HCV infection ALT levels could fluctuate, with long periods of biochemical remission [17]. It has been suggested that at least two different subsets of HCV carriers exist: patients with wide temporal ALT fluctuations, that could be within the normal range for several months, and true ‘biochemically silent’ carriers, showing persistently normal ALT values [18]. It is not known whether these subgroups have different natural history and disease progression [11].

P.: Does it mean that having only two ALT determinations, it is not possible to define my case as HCV carrier with consistently normal ALT?

D.: Unfortunately not, Ms Worry. Former Consensus Conferences [13–15] suggested that the definition of HCV carriers with PNALT should be made on the basis of at least three normal ALT values 2 months apart over a 6-month period. However, more recent prospective studies [17,19] have shown that many subjects referred to as HCV carriers with PNALT on the basis of this definition could have ALT flare-ups during the follow-up, thus proving that even prolonged observation periods might not be adequate to distinguish patients with persistent or transient ALT normality. Thus the observation period should not be shorter than 12–18 months, and ALT determinations should be performed every 2–3 months [11].

P.: Ugh! It means that I must perform ALT determination from time to time! And what about the increase of my ALT values from 20 to 40 IU/L? After all, these values are always within the upper limit of the normal range.

D.: Yes, it is true. However, another important issue concerns the range of ALT ‘normality’ and the definition of the upper limit of the normal (ULN) for patients with chronic hepatitis C. The concept of ‘normal’ ALT remains highly arbitrary [20] and the precise meaning of UNL has not been defined [21]. Recent studies suggest that normal values currently used in clinical chronic hepatitis C ALT levels can be influenced by several other factors, such as alcohol consumption, body weight, gender, age, non-alcoholic fatty liver [22].

P.: Doctor, I would like to try to resume my condition. I have anti-HCV positivity, HCV RNA positivity (although the level of viral load does not correlate with the severity of my liver disease), and I have normal ALT levels over only two determinations, thus you cannot know if I’m an “healthy” carrier, an HCV carrier with persistently ALT levels but possible liver damage or a true patient with transient biochemical remission. Isn’t it?
D.: It is correct. Unfortunately, normal does not always mean healthy.
P.: What means that?
D.: The prevalence of HCV carriers with normal liver (the true ‘healthy’ HCV carriers) seems to be very low (from 0 to 20%) [23–26]. 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 [23,24] although the association of normal ALT with cirrhosis [17,18] or with hepatocellular carcinoma [27,28] has been reported. In all studies, liver histology was, on average, significantly less severe in subjects with PNALT than with abnormal ALT. A recent European Collaborative Study [29] reported that an important proportion of carriers with PNALT had some histological signs of fibrosis, sometimes severe, and in rare cases cirrhosis was found.
P.: Carcinoma? You say that I might run the risk of having liver cancer?
D.: The natural course of HCV infection in patients with normal ALT levels is actually not well understood, as only few studies exist. However, overall data from the literature seem to show that HCV carriers with normal ALT have mild and stable disease, with a favourable prognosis.
P.: Lovely!
D.: Progression of liver disease has been shown by repeat biopsy conducted after approximately 4–7 years’ follow-up, indicating deterioration in up to 23% of individuals [5]. Although progression has not been noted in all studies, this may be due to duration of follow-up, as progression of liver disease in these patients can occur over extended periods. Cross-sectional and longitudinal studies have demonstrated progression of liver disease in patients with normal ALT that, although slower than reported in patients with elevated ALT, still advances at approximately 50% of the rate of patients with elevated ALT [9].
P.: Excuse my question, Doc: but if ALT levels do not correlate with the severity of liver disease, if HCV RNA levels do not predict the persistence normality of liver biochemistry... it means that biopsy is the only tool to ascertain whether the liver is healthy or diseased?
D.: You know, there are three important reasons for performing a liver biopsy: it provides helpful information on the current status of the liver injury, it identifies features useful in the decision to embark on therapy, and it may reveal advanced fibrosis or cirrhosis [5,30]. Without a biopsy, it is difficult to distinguish healthy carriers from those with chronic hepatitis C and normal ALT [9,11].
P.: I would not to contradict your words Doc, but I have read that non invasive tools to evaluate liver fibrosis do exist.
D.: Actually, the recently developed transient elastography that uses ultrasound and low frequency elastic waves to measure liver elasticity has improved the ability to define the extent of fibrosis without a liver biopsy in HCV persons with normal ALT, particularly when combined with other non invasive markers [31]. However, it is not yet ready to replace the liver biopsy, the failure rate is higher in obese patients, and there is now evidence that the transient elastography score can be unexpectedly increased in persons with high necroinflammatory activity but no or minimal fibrosis [5].
P.: In summary, you say I should undergo liver biopsy in order to stage accurately the degree of the fibrosis of my liver? And after biopsy, you could offer me some treatment, I hope!
D.: Slowly, Ms Worry. It is not so easy. The role of liver biopsy in these patients is still highly disputed and consensual recommendations are lacking. These uncertainties probably depend on the poor knowledge of the natural history and the lack of solid evidence for the treatment of persons with normal ALT and chronic HCV infection. Experts still differ on whether to biopsy these patients [5,12–16] in fact, although some of these subjects have marked liver damage at biopsy, the findings that the majority of HCV carriers with PNALT show weaker histologic activity and fibrosis [11] and that the progression rate of fibrosis is significantly slower than in patients with elevated ALT, make it difficult to recommend routine liver biopsy for all HCV carriers with PNALT [7]. Furthermore, biopsy is an invasive procedure with risk of serious complications, economic costs and poor patient compliance [30].
P.: I’m not sure to have fully understood your talk. Without a biopsy, you cannot know the actual histological condition of my liver, but without the knowledge of this finding you cannot offer antiviral treatment. By the way, does a treatment exist? If so, does such treatment differ for patients with normal or abnormal ALT levels?
D.: The currently recommended therapy of chronic HCV infection is the combination of a pegylated interferon alfa and ribavirin [5,10,12]. However, it might be taken into account that 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 earliest guidelines [13,14] discouraged interferon (IFN) treatment in patients with PNALT except in clinical trials because most have low-grade liver fibrosis and are at low risk of disease progression, because of the cost and side effects of therapy, and because of the low response rates to IFN monotherapy (<10–15%) with a risk of ALT flares in up to 50% of patients during treatment. Given these findings, it was concluded that IFN treatment in subjects with PNALT was not beneficial and may actually worsen the underlying disease [13].
P.: Thus, no therapy is recommended in my case?
D.: Don’t worry, many things are changin’ over time. It has been stressed that these patients often show features traditionally associated with a good therapeutic response, such as mild histological lesions, prevalence of females and “easy-to-treat” genotype infection [32]. Finally, given the possibility of ALT flares during follow-up (which invariably accelerate the progression of fibrosis and the worsening of histological activity), the opportuneness of deferring therapy has been questioned because of the possible risk of disease worsening [5,10,33].
P.: Doc, I’m on tenter-hooks. May I have antiviral treatment, or not? And should I undergo biopsy or not? And how many chances of response I have?
D.: At the time of that Consensus Conferences only few trials of IFN monotherapy were available [34–36]. In the last few years, treatment of chronic hepatitis C has progressed from IFN monotherapy to IFN plus ribavirin combination therapy, and more recently to PEG-IFN plus ribavirin. 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 [5].
P.: And thus...?
D.: One multicentre, randomised study [37] of Peg-IFN alpha2a (180 μg weekly) plus ribavirin (800 mg daily) for 24 or 48 weeks in patients with PNALT found an overall sustained virological response (SVR) rate of 30% in those treated for 24 weeks and 52% in those treated for 48 weeks. The response rates in genotype 1b carriers were respectively 13% and 40% and, in those harbouring genotype 2 or 3, they were 72% and 78%. The adverse reactions were no different from those observed in patients with high ALT levels. It should also be stressed that ALT levels actually increased during the one-year follow-up period in more than 50% of the untreated PNALT patients in this placebo-controlled study. However, the subjects with HCV-1 were treated with a fixed RBV dose...
(800 mg/day) that is lower than that universally recommended for such patients (1000–1200 mg/day, depending on body weight).

P.: But if the dose of this drug was lower than that recommended…?

D.: Simulation studies suggest that the SVR rate significantly increases in HCV-1 patients with PNALT when the standard weight-adjusted dose of RBV is administered [38]. A more recent Italian retrospective multicentre study observed an SVR rate of 67% in HCV-1 patients with PNALT treated for 48 weeks with standard RBV doses [39].

P.: Thus, I could hope to have sustained response to treatment! But what is meant by HCV-1, 2, 3,…? Do different types of hepatitis C virus exist?

D.: The hepatitis C virus can be classified into at least 6 major genotypes (genotypes 1 to 6) based on a sequence divergence among isolates [5]. Genotype 1 (subtypes 1a and 1b) is the most common in the U.S. and Europe, followed by genotypes 2 and 3. HCV genotyping should be performed in all HCV-infected persons prior to interferon-based treatment in order to plan for the dose and duration of therapy and to estimate the likelihood of response.

P.: HCV type is 2a.

D.: Well, in your case treatment will last 24 weeks, while in persons with genotypes 1 and 4 up to 48–72 weeks of treatment are required. P.: …and if over the next months my ALT levels will show an abrupt increase, should treatment schedule be reinforced or modified?

D.: The treatment regimen for HCV-infected persons with normal aminotransferase levels should be the same as that used for persons with elevated serum aminotransferase levels [5–10–12]. Thus, regardless of ALT levels, treatment decisions should be individualized based on the severity of liver disease, the potential for serious side effects, the likelihood of treatment response, the presence of co-morbid conditions, and the patient’s readiness for treatment [12]. In particular, decision making should rely on individual patient features, such as genotype, histology, age of the patient, potential progression of disease, probability of viral eradication, co-morbid illness and co-factors, risk of HCV transmission, patient motivation, desire for pregnancy, quality of life and social or psychological stigma, major concerns over infectivity, etc. [11].

P.: Now all is going to be more and more clearer, but I still do not understand if liver biopsy in my case is needed or not.

D.: The earlier views that persons with HCV infection and persistently normal aminotransferase values did not require a liver biopsy because they were believed to have minimal liver disease, and that treatment may actually be harmful, are no longer valid [5].

P.: And so…?

D.: So, the decision to perform a liver biopsy should be based on whether treatment is being considered, taking into account the estimated duration of infection and other indices of disease progression (e.g., the platelet count), the viral genotype, and the patient’s willingness to undergo a liver biopsy and motivation to be treated [39].

P.: Doc, you should consider that I am young, lean, female, with “easy-to-treat” genotype, low viral load, normal ALT levels, well motivated, without co-morbidities, with longer life expectancy… why should I have a biopsy?

D.: Perhaps you are right. Indeed a different algorithm has been recently proposed, based on age, genotype, personal motivation and costs. According to this approach, antiviral treatment might be offered without the need for liver biopsy in patients with a high likelihood of achieving an SVR (e.g. an age of <50 years + easy-to-treat HCV genotype + low viral load), in the absence of any contraindication and co-factors of poor responsiveness [40].

P.: This is my case! Luckily!

D.: Yes, of course. On the contrary, in patients harbouring HCV type 1 or 4 (regardless of age) or in older patients (regardless of HCV type), liver biopsy (or non invasive evaluation of liver fibrosis) might be invariably offered to decide the need for therapy, with treatment recommended only for patients with evidence of liver disease (≥F2) and a higher possibility of response, depending on the HCV genotype [41]. Older patients are at greater risk of disease progression and are likely to be excluded from future transplant programs, hence treatment may be appropriate, although the cost-benefit may be lower. Biopsy and therapy are not recommended in elderly (>65–70 years), [39–41].

P.: and in patients without or with minimal fibrosis?

D.: In these subjects ALT and blood count should be monitored every 4–6 months, avoiding alcohol, hepatotoxins, obesity and liver steatosis. Antiviral treatment should be taken into consideration in these patients in the case of ALT flares, US abnormalities or platelet count decrease [42–44]. Of course, as I said before, measurement of serum HCV RNA level is not recommended because HCV viraemia is not correlated with disease progression [11].

P.: Thank you very much, Doctor Calm. I hope you will follow me in case I’ll decide to undergo antiviral treatment for my liver disease… or should it be simply defined as an “unhealthy liver state”?

Learning points

• Approximately 30% of patients with chronic HCV infection show persistently normal ALT levels.

• The majority of these patients have some degree of histological liver damage that may be significant in up to 20% of patients and might progress toward more severe degree of liver fibrosis.

• The advent of new therapeutic options (pegylated interferons plus ribavirin) has shifted treatment targets toward eradication of underlying infection, regardless of ALT levels.

• Liver biopsy is no longer considered useful in “easy-to-treat” patients (non-1 HCV genotype, female gender, low viral load, persistently normal ALT levels, and lean).

References


