REVIEW

Should we treat HCV carriers with normal ALT levels?
The ‘5Ws’ dilemma

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SUMMARY. Approximately 30% of patients with chronic HCV infection have 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 cases and might progress towards a more severe degree of liver fibrosis. A significant proportion of patients experience periods of increased serum ALT 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 noninvasive tools for the assessment of liver fibrosis, the natural history and the usefulness of antiviral treatment. The advent of new therapeutic options (pegylated interferon plus ribavirin) has shifted treatment targets towards the eradication of underlying infection, with therapy decision based on age, severity of disease and likelihood of response rather than on aminotransferase levels. This review is aimed at approaching the main unresolved issues on this topic, trying to give evidence-based answers to the more frequently asked questions from patients and their physicians.

Keywords: ALT, HCV, interferon, normal, ribavirin.

Up to 30–40% of patients with chronic hepatitis C virus (HCV) infection have persistently normal alanine aminotransferase (ALT) levels (PNALT) [1–5]. Although formerly referred to as ‘healthy’ or ‘asymptomatic’ HCV carriers [6], it has now become clear that the majority of these patients have some degree of histological liver damage [6–11].

Liver damage is usually mild, and fibrosis is generally absent or minimal [1,2,12–14]; however, the association of normal ALT with more severe chronic hepatitis (CH) or cirrhosis has been reported [15–17]. Moreover, the natural course of HCV infection in patients with normal ALT levels is actually not well known. While some studies showed that HCV carriers with normal ALT have mild and stable disease [7,18–20], others reported a significant progression of fibrosis in approximately 20–30% of such patients [21–25].

The development of hepatocellular carcinoma (HCC) in some cases has also been described [26,27]. Sudden worsening of disease with ALT increase and histological deterioration has been reported after many years of follow-up [28].

Whether patients with chronic hepatitis C (CHC) and normal ALT should be offered antiviral treatment in clinical practice has been the subject of an ongoing debate [1,2,16]. Interferon (IFN) treatment is associated with important side effects and is rather expensive. Thus, the first Consensus Conferences on HCV discouraged the treatment of these subjects outside clinical trials [13,14]. The introduction of the new combination therapy of peginterferon (PEG-IFN) plus ribavirin (RBV) results in higher response rates, with a favourable risk/benefit ratio also in patients with benign or slow progressive disease [1,2,16].

In this review, we would examine the main open issues in the management of these so-called healthy subjects, chronically infected with HCV, on the basis of a modified ‘5 Ws analysis’: why, who, when, which and what.

WHY SHOULD WE TREAT HCV CARRIERS WITH NORMAL ALT?

Despite early supposition that HCV carriers with PNALT should be considered as healthy people with invariably
normal liver, it is now widely accepted that 'normal ALT' does not always mean 'healthy liver' [4]. It has been clearly shown that the majority of these carriers have some degree of liver damage on biopsy [6–10,29–31].

Although necroinflammation and fibrosis are generally usually minimal or mild [12–14,19,20,32], the possibility of more severe CH and cirrhosis has been reported [22,33–36] and the occurrence of HCC has been suggested [26,36], even in patients with otherwise 'healthy' liver [27].

Finally, it is well known that during the course of their disease, HCV carriers may suffer from extrahepatic manifestations, sometimes more severe than the underlying liver disease: lymphoproliferative disorders, mixed cryoglobulinemia, thyroid disorders, sicca syndrome, porphyria cutanea tarda, lichen planus, diabetes, chronic polyarthritis, etc. [37].

It should be underlined that the concept of 'normal' ALT remains highly arbitrary [4,16] and that the ALT reference ranges currently used in clinical practice underestimate the actual frequency of liver disease in this subset of patients [17]. It should be considered that actual thresholds were mostly computed from the late 1960s to the 1980s, when ALT testing was introduced as a surrogate marker for the screening of non-A and non-B hepatitis among blood donors. Thus, so-called reference populations were likely to include substantial proportions of individuals with nonalcoholic fatty liver disease or HCV infection, now recognized as the most prevalent causes of chronic liver disease in western countries.

Finally, given the typically fluctuating pattern of ALT levels in chronic HCV infection, only more stringent tests can distinguish subjects with PNALT from those in temporary biochemical remission [1,16]. It is known that during the course of HCV infection, ALT levels could fluctuate, with long periods of biochemical remission [4,7,15–18]. 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 PNALT values [4,8,38]. It is not known whether these subgroups have different natural history and disease progression. Former Consensus Conferences 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 [13,14]. However, more recent prospective studies [7,18–22] have shown that many subjects referred to as HCV carriers with PNALT on the basis of this definition could have ALT flare-ups during follow-up, thus proving that even prolonged observation periods might not be adequate to distinguish patients with persistent or transient ALT normality. It means that the observation period should not be shorter than 12–18 months, and ALT should be determined every 2–3 months [38]. In conclusion, patients with ALT flares during follow-up cannot, by definition, be considered as 'persistently' normal ALT patients, but rather as 'repeatedly' normal ALT patients.

As to the cost/benefit ratio, the impact of antiviral therapy on morbidity and mortality in HCV patients with PNALT has been recently evaluated [39]. Treatment of these patients might significantly reduce 2008–2025 HCV-related morbidity and mortality, despite a probability of receiving treatment that is three to five times less in this population. If these subjects were treated at the same rate as those with abnormal ALT, morbidity and mortality could be further reduced.

The updated AASLD Practice Guidelines [2] suggest that (i) regardless of the serum ALT level, the decision to initiate therapy with PEG-IFN and RBV should be individualized based on the severity of liver disease by liver biopsy, the potential for serious side effects, the likelihood of response, and the presence of comorbid conditions; (ii) The treatment regimen for HCV-infected individuals with normal aminotransferase levels should be the same as that used for individuals with elevated serum aminotransferase levels’ [2].

In summary, the possibility of progression to more severe liver damage despite persistently normal biochemistry, the risk of HCC, the possibility of extra-hepatic diseases and economic considerations suggest that HCV-infected individuals with PNALT should not be excluded a priori from antiviral treatment [40].

WHO SHOULD BE TREATED?

The Medical Position Statement on the management of hepatitis C by the American Gastroenterological Association (AGA) states that ‘decision analyses in patients with biochemically and histologically mild chronic hepatitis C have led to the conclusion that, even in this population, antiviral therapy is cost-effective. Clinicians may rely in their decision making on individual patient features, including patient motivation and perspective, genotype, relative histologic activity and fibrosis, duration of HCV infection, age, occupation, symptoms, and so on’ [16].

Careful evaluation of the individual and viral features is mandatory to assess the actual need for antiviral treatment. In particular, parameters traditionally associated with poor outcome and progression towards more severe liver damage should be watchfully identified.

Available data from the literature indicate that the main factors of progression are as follows: male gender, age >40 years, baseline fibrosis ≥F2, ‘high-normal’ ALT, ALT flares, cofactors, steatosis, overweight and shorter duration of disease [2,16,17,36,38]. Thus, in the presence of one or more of these features, antiviral treatment should be started without delay [21].

However, because of the huge number of HCV patients with PNALT (probably a reflection of the great number of subjects with HCV chronic infection), priority needs to be defined: it is impossible to perform liver biopsy and offer antiviral therapy to all HCV carriers, and the cost of treating all these people would be exceedingly high.

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Cost/benefit ratio might be particularly favourable in:

- young, ‘easy-to-treat’ patients, having high rates of sustained virological response (SVR) (e.g. women, low viral load and HCV non-1);
- middle-aged patients with ‘significant’ liver disease and/or possible cofactors of progression of liver damage, thus at risk of developing end-stage liver disease [28,40].

The age issue has a critical role in decision making [40]. Younger patients have a higher chance to achieve SVR and tolerate therapy better; they have longer life expectancy, are often well motivated, usually have minimal disease and have fewer contraindications. Thus, in this group, the decision to treat should be based more on the expected response and motivation than on the severity of liver disease [15].

On the contrary, older patients respond less well to therapy, more frequently have significant liver disease and/or cofactors, often have longer infection/disease duration, may experience more side effects and might be less motivated. Thus, in this group, decision to treat should be based on the severity of liver disease and on the possibility of achieving a sustained response [1,2,15,16,40].

A recent Italian Expert Opinion Meeting suggested the following recommendations [38]:

1. HCV carriers with PNALT may receive antiviral treatment with PEG-IFN plus RBV using the same algorithms recommended for HCV patients with abnormal ALT levels.
2. Decision making should rely on individual characteristics such as genotype, histology, age, potential disease progression, the probability of viral eradication, patient motivation, the desire for pregnancy, comorbidities and cofactors.
3. Antiviral treatment might be offered without the need for liver biopsy in patients with a high likelihood of achieving an SVR (e.g. age <50 years + easy-to-treat HCV genotype + low viral load), in the absence of any contraindications and cofactors.
4. In patients aged 50–65, and in those with a reduced likelihood of achieving an SVR, a liver biopsy may be used to evaluate the need for therapy, with treatment being recommended only for patients with more severe fibrosis (>F2) and a higher possibility of response. Biopsy and therapy are not recommended in the elderly (>65–70 years).
5. Noninvasive assessments of fibrosis can be made to detect changes over time and consequently indicate the need for biopsy or treatment on an individual patient basis.

WHEN ANTIVIRAL TREATMENT SHOULD BE STARTED?

A crucial issue in clinical practice is the timing of antiviral treatment. When managing HCV carriers with PNALT who are candidates for antiviral treatment, it should be decided whether therapy should be immediately started or whether these patients might be followed up before offering treatment. Three diagnostic scenarios can be seen:

1. A patient who has just been found to be anti-HCV positive with ‘normal’ ALT (sporadic determinations).
2. A patient who has been referred as being anti-HCV positive with ‘normal’ ALT on 1 or more occasions in the last 6 months.
3. A patient known to have been anti-HCV positive with ‘normal’ ALT for a long period of time [15].

The decision to treat or not to treat should be based on the knowledge of the natural history in the single case. Several studies reported that both activity and fibrosis remained unchanged in HCV patients with PNALT after an average follow-up of 3.5–5.0 years [7,18], while others showed a significant progression of fibrosis in 20–30% of the patients with PNALT [25,32,34]. Sudden worsening of disease with ALT increase and histological deterioration has been described after many years of follow-up [34,41,42].

A greater risk of ALT flares and a more rapid progression to fibrosis has been reported in patients infected with HCV-2 [28].

In conclusion, the natural history of HCV carriers with PNALT is probably not always benign, and the possibility of a more severe evolution of liver disease in this subset of patients cannot be ruled out. Several features should be taken into account to decide treatment timing: age, risk of progression, probability of response, liver damage, willingness to be treated, major concerns over infectivity and desire for pregnancy [2,16]. The effectiveness of deferring therapy has been questioned because of the risk of disease worsening and of HCC occurrence, the possible development of contraindications to antiviral treatment during the follow-up and the possible occurrence with the ageing of comorbidities which finally prevent antiviral treatment.

WHICH TREATMENT SHOULD BE PRESCRIBED?

Earliest guidelines discouraged routine antiviral treatment in patients with PNALT [13,14], because of the costs of therapy, the incidence of side effects, the low response rates and the risk of ALT flares during treatment. IFN-alpha monotherapy allowed SVR in approximately 15–23% of the cases [43–49]. ALT flares during the treatment or the follow-up were reported in approximately 47% of patients, raising concerns regarding the risk of conventional IFN monotherapy compared with only modest benefit [13,14].

The introduction of the combination of PEG-IFN plus RBV has led to response rates ≥50%, with a favourable risk/benefit ratio even in patients with slowly progressing disease [2,16]. The first study of PEG-IFN alpha-2a (180 µg weekly) plus RBV (800 mg daily) reported an SVR of 40% in HCV-1 carriers with PNALT treated for 48 weeks and of 72% in HCV-2 and HCV-3 carriers treated for 24 weeks [50].
However, in this study, HCV-1 patients were treated with a fixed RBV dose, lower than that recommended for these patients. Simulation studies [51] suggested that the SVR rates might significantly increase in HCV-1 patients when the standard weight-adjusted dose of RBV is administered.

The efficacy of antiviral treatment was confirmed in clinical practice in a recent study [52]. All PNALT patients received PEG-IFN alpha-2a 180 mg weekly plus RBV 800 mg/day for 24 weeks (HCV-2 and HCV-3) or 1000–1200 mg/day for 48 weeks (HCV-1). SVR was seen in 62% of HCV-1 patients, 89% of HCV-2 and 80% of HCV-3 patients.

The importance of a rapid virological response (RVR) as a predictor of sustained viral clearance was further evaluated in 115 patients with PNALT [53]. RVR was observed in 68% of the patients (42% patients with HCV-1, 90% HCV-2 and 64% HCV-3). Overall, 92% of patients with RVR achieved HCV eradication vs 38% of those without RVR.

Finally, a 2-log drop in HCV RNA at day 28 has been identified as the best predictor of SVR in patients with HCV-1 and PNALT treated with PEG-IFN alpha-2b plus RBV [54], and the possibility of high SVR following extremely short antiviral treatment (4–6 weeks) has been reported in a selected population of women with HCV-2 infection and PNALT [55].

WHAT SHOULD BE EXPLAINED TO HCV CARRIERS WITH PNALT?

Given the uncertainties still existing when managing these ‘unhealthy’ subjects in clinical practice [56], an understandable dialogue between doctors and their HCV patients with PNALT is mandatory to give clear and evidence-based answers to the more frequently asked questions [15].

Anti-HCV testing in individuals with normal ALT

The majority of carriers with PNALT discover their HCV positivity by chance [15]. Usually, anti-HCV testing is performed because of blood donations, screening of relatives of HCV patients, hospitalizations, endoscopic procedures, day surgery, etc. [17,38]. Even in the absence of ALT abnormality, HCV screening should be recommended for individuals who have injected illicit drugs in the past, people infected with HIV/HBV, prior recipients of transfusions, clotting factors, organ transplants, etc., those ever on haemodialysis, children born to HCV-infected mothers, health care, household or sexual partners of HCV-infected individuals [2,16]. Except for these cases, mass screening is unjustified and not cost effective [57,58].

Screening of relatives

Although the prevalence of infection among household and sexual partners of PNALT is very low [59]. HCV prevalence in these groups was found to be significantly higher compared with controls [60]. Thus, a negative test in the partner and children of HCV cases with PNALT provides reassurance, making testing of relatives of benefit in clinical practice [2,16].

Viral load and liver damage

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 [17,38,61]. Thus, repeated quantitative determination of viraemia should be discouraged, as it might increase the anxiety of the patients [17,38]. In clinical practice, HCV RNA should be detected: (i) to distinguish between ‘true’ HCV carriers with normal ALT and anti-HCV-positive/HCV RNA-negative individuals, as the latter may represent more commonly recovery from HCV infection [2] and (ii) in patients for whom antiviral treatment is being considered, to determine the likelihood of response [38].

Significance of ALT ‘normality’

As underlined earlier, the precise cut-off of ALT ‘normality’ remains arbitrary [62]. ALT levels can be influenced by several factors, such as alcohol consumption, body weight, gender, age and steatosis [63]. Several studies suggest that existing ‘normal’ ALT thresholds are too high [62] and should be lowered by 25–30%, thus setting the ‘optimal’ ALT threshold at 30 U/L for men and 20 U/L for women [17].

Liver biopsy vs noninvasive tools

Experts still differ on whether to biopsy patients with PNALT [1,2,16]. These uncertainties probably depend on the poor knowledge of the natural history and the lack of solid evidence for the treatment of individuals with normal ALT and chronic HCV infection [64]. There are three important reasons for performing a liver biopsy in HCV carriers with normal ALT: it provides helpful information on the current status of liver injury, it identifies features useful in the decision to embark on therapy and it may reveal advanced fibrosis or cirrhosis [65]. Without a biopsy, it is difficult to distinguish true ‘healthy’ carriers from those with CHC and PNALT [64].

However, it is difficult to recommend routine biopsy for all HCV-PNALT [38,56]. The decision to perform a biopsy in PNALT should be based on whether treatment is being considered, taking into account the estimated duration of infection, probability of disease progression, willingness to undergo a liver biopsy, motivation to be treated and availability of noninvasive tools to assess liver fibrosis. The recently developed transient elastography technique has improved our ability to non-invasively define the extent of
fibrosis in HCV persons [11]. However, the elastography score can be unexpectedly increased in individuals with high necroinflammatory activity but not in none or minimal fibrosis [66].

Follow-up of patients not candidates to antiviral treatment

In these subjects, follow-up might be continued over time, and ALT and blood count should be monitored every 4–6 months [17]. It should be strongly recommended to them to avoid alcohol, obesity and liver steatosis. In particular, being overweight might be corrected [17,38]. It is not clear whether these subjects should be routinely offered anti-HBV vaccine, given the risk of disease progression in the case of de novo HBV infection [17].

During follow-up, antiviral treatment should be reconsidered in the case of ALT flares, US abnormalities or platelet count decrease [38,67]. As mentioned earlier, repeated measurements of serum HCV RNA to evaluate disease progression is not recommended [61].

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