

Antiviral treatment of Hepatitis C Virus Carriers with normal ALT levels: actual utility or unnecessary expense?

Claudio Puoti

Many subjects with chronic Hepatitis C Virus (HCV) infection show persistently normal alanine aminotransferase (ALT) levels (PNALT),¹⁻⁴ and thus formerly defined as 'healthy' or 'asymptomatic' HCV carriers.¹ However, it is now clear that only a minority of these people show normal liver (15-20%).⁵⁻⁷ Therefore, 'normal ALT' does not always mean 'healthy liver.'⁴

It is known that during the course of HCV infection ALT levels could fluctuate widely, with long periods of biochemical remission.¹⁻⁴ Thus, at least two different subsets of HCV-PNALT carriers exist: patients with temporal ALT fluctuations, that could be within the normal range for several months, and true 'biochemically silent' carriers showing persistently normal ALT values.⁴ It means that the observation period should not be shorter than 12 - 18 months, and ALT determinations should be performed every 2 - 3 months.^{4,6}

Although liver damage is usually mild,^{1,2} the presence of more severe chronic hepatitis (CH) or cirrhosis has been reported despite consistently normal liver biochemistry.⁸ Although some studies showed that HCV carriers with normal ALT have mild and rather stable disease, others reported a significant progression of fibrosis in approximately 20-30% of the patients with ALT normality.⁹ The development of hepatocellular carcinoma (HCC) has been also described.¹⁰ Sudden worsening of disease with ALT increase and histological deterioration has been reported after many years of follow-up.¹¹

Finally, HCV carriers with PNALT may suffer from extra-hepatic manifestations, sometimes more severe than the underlying liver disease: lymphoproliferative disorders, mixed cryoglobulinaemia, thyroid disorders, sicca syndrome, porphyria cutanea tarda, lichen planus, diabetes, chronic polyarthritis, etc.^{1,2,12}

Therefore, 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 persons with

PNALT should not be excluded *a priori* from antiviral treatment.^{1,2}

The earliest guidelines discouraged interferon (IFN) treatment in patients with PNALT because of the cost and side effects of therapy,^{1,2} and of the low response rates to IFN monotherapy (<10-15%) with a risk of ALT flares in up to 50% of patients during treatment.⁹

The introduction of the combination of weekly subcutaneous pegylated-IFN (PEG-IFN) plus daily oral ribavirin (RBV) has led to response rates $\geq 50\%$, with a favourable risk-benefit ratio even in patients with slowly progressing disease.^{1,2,9} The first trial of PEG-IFN plus RBV found a sustained virological response (SVR) in 40% of HCV-1 carriers with PNALT treated for 48 weeks, and in 72% of HCV-2 and HCV-3 treated for 24 weeks.¹³ The efficacy of antiviral treatment with PEG-IFN plus RBV was subsequently confirmed in clinical practice.^{14,15}

However, in everyday practice, management of carriers with PNALT may be paradoxically more difficult than that of patients with abnormal ALT levels. Indeed, it is not always so easy to ascertain in the single case whether it should be considered as healthy subject or true patient. Several topics to date remain unresolved: Should these 'seemingly healthy' people undergo routine liver biopsy? Is antiviral treatment justified in 'asymptomatic' subjects with persistently normal liver biochemistry? Is long-term follow-up needed in this setting, and how long it should last?²

Liver biopsy provides helpful information on liver damage, as it may reveal the presence of advanced fibrosis or cirrhosis. Without a biopsy, it is impossible to clinically distinguish true 'healthy' carriers from those with CH.⁴ On the other hand, it is difficult to recommend routine biopsy for all HCV-PNALT.⁴ The decision to perform a biopsy 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 biopsy, motivation to be treated, and availability of non-invasive tools to assess liver fibrosis.¹² The recently developed transient elastography has improved our

ability to non-invasively define the extent of fibrosis in HCV persons.⁵

Careful evaluation of parameters associated with disease progression is mandatory to assess the actual need for antiviral treatment.⁴ Indeed, it is really impossible to suggest antiviral therapy in *all* HCV carriers, as the costs would be exceedingly high, due to the high number of HCV patients with PNALT. Data from the literature indicate that the main factors of progression are male gender, advanced age, severe fibrosis, ALT flares, and steatosis.¹⁻²

Cost/benefit might be particularly favourable in:

- Young patients, having high rate of SVR (e.g. females, low viral load, HCV genotype non-1, etc).
- Middle age patients with 'significant' liver disease and/or co-factors of progression of liver damage, thus at risk of developing more severe liver disease.¹²

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

On the contrary, older patients respond less well to therapy, are more likely to have significant liver disease and/or co-factors, could experience more side effects and may be less motivated. Thus, in this group decision to treat should be based on the severity of liver disease and on the possibility of SVR.

A recent Italian Expert Opinion Meeting suggested the following recommendations:¹²

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.*
2. *Decision making should rely on individual characteristics such as HCV genotype, histology, age, potential disease progression, probability of eradication, patient motivation, desire for pregnancy, co-morbidities, co-factors, etc.*
3. *Treatment might be offered without liver biopsy in patients with a high likelihood of SVR (e.g. age <50 years + non-1 HCV genotype + low viral load), in the absence of co-factors of poor responsiveness.*
4. *Inpatients aged 50–65 years, and in those with a reduced likelihood of achieving a response, biopsy may be used to evaluate the need for therapy, with treatment being recommended only for patients with more severe fibrosis and higher possibility of SVR. Biopsy and therapy are not recommended in the elderly (>65-70 years).*

In patients who are not candidates for antiviral treatment, follow-up may be continued, and ALT should be monitored every 4-6 months. Avoidance of alcohol and obesity may be

strongly recommended.¹² It is not clear whether these subjects should be routinely offered anti-HBV vaccine, given the risk of disease progression in the case of HBV infection.¹² Antiviral treatment should be re-considered in the case of ALT flares, US abnormalities or platelet count decrease. Repeated measurements of serum HCV RNA to evaluate disease progression is not recommended.^{1, 9, 11, 12}

Competing Interests

None declared

Author Details

CLAUDIO PUOTI, MD, Chief, Dept. of Internal Medicine and Hepato-Gastroenterology, Marino General Hospital, Marino, Rome, Italy
CORRESPONDENCE: CLAUDIO PUOTI, MD, Chief, Dept. of Internal Medicine and Hepato-Gastroenterology, Marino General Hospital, Via XXIV Maggio, 00047, Marino, Rome, Italy
Email: puoti@epatologia.org

REFERENCES

1. Strader DB, Wright T, Thomas DL, et al. Diagnosis, management and treatment of hepatitis C. AASLD practice guideline. *Hepatology* 2004;39:1147–1171.
2. Ghany MG, Strader DB, Thomas DL, et al. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology* 2009;49:1335–1373.
3. Puoti C. Hepatitis C with normal aminotransferase levels. *Dig Dis* 2007;25:277–278.
4. Puoti C. HCV carriers with persistently normal aminotransferase levels: normal does not always mean healthy. *J Hepatol* 2003;38:529–532.
5. Castera L, Foucher J, Bertet J, et al. FibroScan and FibroTest to assess liver fibrosis in HCV with normal aminotransferases. *Hepatology* 2006; 43: 373-4
6. Puoti C, Bellis L, Guarisco R, et al. HCV carriers with normal alanine aminotransferase levels: healthy persons or severely ill patients? *Eur J Intern Med* 2010;21:57-61.
7. Martinot-Peignoux M, Boyer N, Cazals-Hatem D, et al. Perspective study of anti hepatitis C virus-positive patients with persistently normal serum ALT with or without detectable serum HCV RNA. *Hepatology* 2001;34:1000–1005.
8. Puoti C, Castellacci R, Montagnese F, et al. Histological and virological features and follow-up of HCV carriers with normal aminotransferase levels: the Italian prospective study of the asymptomatic C carriers (ISACC). *J Hepatol* 2002;37:117-123
9. Dienstag JL, McHutchison JG. American Gastroenterological Association [AGA] Medical Position Statement on the Management of Hepatitis C. *Gastroenterology* 2006;130:225–264.
10. Puoti C, Bellis L, Martellino F, et al. Occurrence of hepatocellular carcinoma in an apparently 'healthy' HCV patient. *Eur J Gastroenterol Hepatol* 2005;17:1263-1264.
11. Puoti C, Guido M, Mangia A, et al, for the Italian Association for the Study of the Liver. Clinical management of HCV carriers with normal ALT levels. *Committee Digest Liver Dis* 2003;35:362–369.
12. Puoti C, Coppola N, Toti M, et al. Treatment of patients with normal ALT levels. In Practice guidelines for the treatment of hepatitis C: Recommendations from an Expert Opinion Meeting. *Digest Liver Dis* 2010;42:81-91.

13. Zeuzem S, Diago M, Gane E, et al. Peginterferon alpha-2a [40KD] and ribavirin in patients with chronic hepatitis C and normal aminotransferase levels. *Gastroenterology* 2004;127:1724-1732.

14. Puoti C, Pellicelli A, Romano M, et al. Treatment of hepatitis C virus carriers with persistently normal alanine aminotransferase levels with Peginterferon alfa-2a and ribavirin: a multicentric study. *Liver Int* 2009;29:1479-1484.

15. Puoti C, Barbarini G, Picardi A, et al. Rapid virological response as a predictor of sustained response in HCV-infected patients with persistently normal alanine aminotransferase levels: A multicenter study. *J Viral Hepat* 2011 (in press,doi:10.1111/j.1365-2893.2010.01319.x).
