The management of patients with mild hepatitis C

C. Verslype[1,*], P. Michielsen[2,*], M. Adler[3,*], H. Orlent[4,*], D. Sprengers[5,*], J. Delwaide[6,*], F. D'heygere[7], Ph. Langlet[8,*], R. Brenard[9,*], I. Colle[10], H. Reynaert[11,*], P. Stärkel[12,*], J. Henrion[13,*]

(1) Department of Hepatology, University Hospital Gasthuisberg, Leuven, Belgium ; (2) Department of Gastroenterology and Hepatology, University Hospital Antwerp, Belgium ; (3) Department of Gastroenterology and Hepatology, University Hospital Erasme, Brussels, Belgium ; (4) Department of Gastroenterology and Hepatology, AZ Sint-Janshospitaal, Brugge, Belgium ; (5) Department of Gastroenterology and Hepatology, Sint-Augustinusziekenhuis, Antwerp, Belgium (6) Department of Gastroenterology and Hepatology, University Hospital, Liège, Belgium ; (7) Department of Gastroenterology and Hepatology, Groeninghe Hospital, Kortrijk, Belgium ; (8) Department of Gastroenterology and Hepatology, CHU Brugmann and CHIREC-Cavell, Brussels, Belgium ; (9) Department of Gastroenterology and Hepatology, Hôpital Saint-Joseph, Gilly, Belgium ; (10) Department of Gastroenterology and Hepatology, University Hospital Gent, Belgium ; (11) Department of Gastroenterology and Hepatology, University Hospital Free University of Brussels, Belgium ; (12) Department of Gastroenterology and Hepatology, University Hospital Saint-Luc, Brussels, Belgium ; (13) Department of Gastroenterology and Hepatology, Hôpital Jolimont, Haine-Saint-Paul, Belgium.

Abstract

Infection with the hepatitis C virus (HCV) represents an important public health problem and is a leading cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma. Chronic hepatitis C is a heterogeneous disease. Many patients have mild disease at presentation but not all of them will develop advanced liver disease. However, the identification of these patients with mild hepatitis C who will show progressive disease is difficult and is based on histological criteria and the assessment of co-factors (age, alcohol intake, steatosis). In addition, serum transaminases that are persistently normal on several occasions during 18 months may point to a more benign course. Patients with mild hepatitis C should not be excluded "a priori" from the possibility of being treated, as treatment with pegylated interferon and ribavirin is safe and effective in this group. Overall, the decision to initiate therapy should be individualized and based on the severity of the disease by liver biopsy, the potential of serious side effects, the probability of response and the motivation of the patient. (Acta gastroenterol. belg., **2005**, 68, **314-318**).

Key words : persistently normal ALT, mild hepatitis C, liver biopsy.

Introduction

Infection with HCV is a leading cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma. The natural history of HCV infection is not fully understood. Following acute infection, between 55 and 85% of patients will develop chronic hepatitis, depending on the age of the patients, immunogenetic factors and size of the inoculum. The course of the chronic infection is variable (1). More than 50% of patients have mild disease and a subset will develop cirrhosis and its complications. A consensus development meeting on the management of mild hepatitis C was organized in Spa on February 26th 2005, during the XVIIth Belgian Week of Gastroenterology. The topic was introduced by two experts : S. Zeuzem (Homburg/Saar, Germany) and Y. Horsmans (UCL, Woluwe, Belgium) and followed by discussion with the audience. This article is a consensus document prepared by a Belgian working group consisting of hepatogastroenterologists from academic and non academic centres.

Definition of mild chronic hepatitis C

The severity of chronic hepatitis C can be assessed clinically, by biochemical tests or histological findings. Most often, chronic hepatitis C is either defined as those patients who are asymptomatic with normal serum ALT levels or as those with mild histologic lesions, irrespective of serum ALT (2). A definition which takes into consideration different parameters may be more appropriate, thus helping us in selecting those patients who will benefit most from antiviral treatment.

The role of clinical symptoms

Independently from the liver damage, HCV infection can seriously interfere with quality of life through disabling symptoms such as fatigue, malaise, bodily pain, depression cognitive symptoms and extrahepatic manifestations (such as mixed cryoglobulinemia leading to potentially severe neurological,cutaneous and nephrological complications) (3).

The role of serum aminotransferases

Serum aminotransferases have been used in the clinic to distinguish those with mild and severe chronic hepatitis C. Recent population-based studies indicate that around 40% of HCV chronically infected individuals have persistently normal ALT (PNALT) values when tested serially during a 6-month observation period (4). However, there are important limitations to the use of these liver enzymes, as they may be normal in the presence of significant liver disease. This is illustrated by a recent Korean study, that showed a positive association between high-normal serum ALT (34-40 IU/L) levels

* Steering Committee of the Belgian Association for the Study of the Liver (BASL).
Correspondence : Prof. Dr. C. Verslype, Department of Hepatology, University Hospital Gasthuisberg, Herestraat 49, 3000 Leuven, Belgium.
E-mail : Chris.Verslype@uz.kuleuven.ac.be.

Table 1. — **Progression of fibrosis in untreated patients with chronic hepatitis C and initial stage F0/F1 in liver biopsy**

Number of patients	Interval (mean) between biopsies (yrs)	% with fibrosis progression	% with severe fibrosis (≥ F3)	Reference
110	3.2	32	2	Marcellin *et al.* 2002 (12)
45	3.8	42	4	Ghany *et al.* 2003 (13)
61	6.3	33	10	Hui *et al.* 2003 (14)
106	8.3	60	27	Alberti *et al.* 2004 (2)

and mortality from liver disease, even after adjustment for alcohol consumption, obesity, plasma glucose en serum lipids (5). It should be emphasized that the definition of 'normal' serum ALT-levels is arbitrary and should be redefined to lower values, excluding obese patients when establishing the normal range (6). In addition, many HCV-infected patients (12 to 27%) with initial normal ALT, develop ALT-flares when submitted to a strict follow-up. The definition of patients with chronic HCV infection and PNALT therefore requires a bimonthly finding of normal ALT during 18 months. Many of the studies on histology and therapy published in the literature have less stringent definitions of normal ALT. To better define these patients Alberti suggested to add indication of the length of observed ALT abnormality (e.g. 6 mo-PNALT, 12 mo-PNALT, etc.) (7). Twenty-two percent of 1154 patients included in 23 studies with PNALT had significant (at least Metavir F2) fibrosis in the liver biopsy. In the recent study by Zeuzem of antiviral treatment in patients with PNALT, 30 % had stage F2 or more (8). In most studies, grading and staging of the liver disease was lower in those patients with normal ALT than in those with elevated ALT (2). Overall, 30-40% of patients with initial normal ALT have or may develop a progressive form of chronic hepatitis C. Follow-up of serum ALT and/or liver histology is required to fully appreciate the risk in the individual patient. However, this follow-up may be cumbersome, costly and even unnecessary when treatment is "a priori" not considered or when very high cure rates can be obtained (genotype 2 or 3 infection, see below).

There is an unmet need for serum markers that can reliably detect the stage of liver fibrosis. Several serum tests are in development, including the fibrotest (based on the combination of simple serum biochemical markers and GlycoCirrho test (based on profiles of serum protein N-glycans (9,10). To date, it is still not clear whether these tests can fully replace liver biopsy. A major advantage of liver biopsy over any serum marker of fibrosis is the additional value of the diagnosis of coexistent alcoholic, nonalcoholic steatohepatitis or drug-induced liver disease.

The role of histology

The severity of compensated chronic hepatitis C is defined according to the extent of necroinflammation (activity) and of fibrosis (staging) in the liver biopsy. So far, the degree of liver fibrosis can only be assessed confidently by a liver biopsy. Mild chronic hepatitis is characterized by no fibrosis or the presence of periportal fibrosis expansion (Metavir F0-F1). The occurrence of portal-portal septa (F2), portal-central septa (F3) and cirrhosis (F4) is considered as a major liver disease. Metavir F2 or more is an important predictor of future progression of liver disease and antiviral treatment is strongly recommended (11).

The prognosis of the mild group (Metavir F0/F1) is heterogeneous and up to 30% of these patients may have progression to cirrhosis (2). Four studies addressed the progression of liver fibrosis (by serial liver biopsies) in untreated HCV infected patients and the results are summarized in Table 1 (2, 12-14). Two of these studies are not published as full paper (2, 12). In the study of Marcellin *et al.* (12), fibrosis progression was seen in only 32% of the patients, only 2% developed severe fibrosis (F3 or F4), after a relatively short mean interval of 3.2 years between the initial and final biopsy. Ghany *et al.* (13) reported progression of fibrosis in 13/21 patients with initially no fibrosis and 18/43 with initially portal fibrosis, over a mean period of 3.6 years between the two biopsies. The risk of progression was significantly higher in patients with elevated ALT compared to patients with persistently normal ALT. Hui *et al.* (14) described fibrosis progression in 20/61 patients with initially F0 or F1 fibrosis over a mean period of 6.3 years. Also here the risk of fibrosis progression was signifacantly ghigher when ALT was elevated. Development of severe fibrosis or cirrhosis was only seen when elevated ALT was present. The Italian study (2) investigated fibrosis progression in 106 patients with mild chronic hepatitis C ; the mean time interval between biopsies was 8.3 years and represented the longest time interval reported so far. Progression of fibrosis was seen in 60% of cases and correlated with an alcohol intake, age at diagnosis, serum ALT flares during follow-up, steatosis and necroinflammatory activity in the initial biopsy.

Consensus definition of mild hepatitis C by the Belgian working group. We propose to define mild chronic hepatitis C by *no or mild fibrosis* (Metavir F0 or F1) in the liver biopsy. In addition, there should be *a low risk of progression of liver fibrosis* and/or no impairment in *quality of life* (e.g. due to extrahepatic manifestations). The evaluation of the risk of progression represents a challenge for the hepatologist. The risk of disease

progression in initially mild chronic hepatitis C with elevated ALT has been estimated by outcome modelling (15) at 4% within 20 years and at 15% within 30 years in cases with F0 in the presenting biopsy, but the corresponding risk increased in patients with F1 in the initial biopsy (30% within 20 years and 60% within 30 years). But also the above mentioned cofactors need to be acknowledged. The risk is considered very low in a young non-obese female patient, abstaining from alcohol, who initially presented with F0 and when serum ALT levels are persistently normal during follow-up. In the case of a male patient with F1 in the initial biopsy, the occurrence of ALT flares, alcohol intake, obesity or liver steatosis, a significant worsening of liver disease can be expected and the denomination of this condition as mild hepatitis C may falsely reassure the patient and the doctor.

Treatment of patients with mild hepatitis C

The efficacy of antiviral treatments for chronic hepatitis C has improved in the last decade due to the implementation of pegylated interferon-alpha plus ribavirin combination therapy. Sustained virological response rates, defined as undetectable HCV-RNA after 24 weeks of treatment-free follow-up, are around 50% for HCV genotype 1 and around 80% for genotype 2/3 (16,17). However, the costs of therapy have also substantially increased and tolerability is not yet optimal (18). Most national (19) and international guidelines (1,11) still recommend that antiviral therapy should be given primarily, if not exclusively, to patients with a "progressive" type of liver disease.

Until recently, patients with chronic hepatitis C and persistently normal alanine aminotransferase levels have been routinely excluded from large randomized treatment trials ; consequently, the efficacy and safety of antiviral therapy in this population are unknown. Zeuzem coordinated a pivotal multinational trial in which patients with at least 3 normal ALT values over an 18-month period were randomized (3:3:1) to treatment with peginterferon alfa-2a 180 µg/wk plus ribavirin 800 mg/day for 24 weeks (212 patients), the same combination for 48 weeks (210 patients), or no treatment (69 patients) (8). All patients were monitored for 72 weeks. The primary endpoint was sustained virologic response (SVR). No patient cleared HCV RNA in the untreated control group. In patients infected with HCV genotype 1, SVR rates of 13% and 40% were obtained with 24 and 48 weeks of treatment, respectively ($p < .0001$). In patients infected with genotypes 2 or 3, SVR rates were 72% and 78% with 24 and 48 weeks of treatment, respectively ($p = 0.452$). Treatment-related flares in ALT activity were not observed. In addition, there was a significant drop in serum ALT levels in those patients who achieved viral erdication. The results of this pivotal trial indicate that the efficacy and safety of peginterferon alfa-2a and ribavirin combination therapy in patients with chronic hepatitis C and PNALT are similar to that in patients with elevated ALT levels. However, the inclusion criteria of the study were based on PNALT and as such not all the patients included in this study had mild hepatitis C according to our previous suggested definition : 30% of patients had a baseline liver histology ≥ F2 (Ishak scoring system) and more than 50% of patients developed mild ALT elevations while on study. The main conclusion from this trial is that the indication for treatment of hepatitis C should therefore be evaluated independently from baseline ALT activity but this trial does not fully answer the question whether we should treat mild hepatitis C.

Some experts still prefer to leave patients with mild hepatitis C without treatment and to monitor them periodically, especially when infected with genotype 1 (20). There are several reasons no to treat patients with mild hepatitis C : most patients do not die due to HCV, the limited response in genotypes 1 and 4, it is not cost effective in older patients, the side effects and costs of the treatment, the psychological impact of absence of antiviral efficacy and the hope for new drugs with a better efficacy/tolerability profile.

On the basis of all these considerations, patients with mild hepatitis C should, however, not be excluded "a priori" from the possibility of being treated. Decisions to treat should be individualized and based on a set of variables, including liver histology, patient age, particular context (professional, desire of pregnancy, clinical symptoms), the HCV genotype and load, as well as comorbidities and contraindications, in agreement with the conclusions of the NIH Consensus Conference on the Management of Hepatitis C (1). In addition, treatment should be considered for those patients who have symptoms and signs suggesting progression from mild to moderate or severe disease. On the basis of these variables a treatment plan should be discussed with the patient, taking into acount the patient's desire to eliminate the virus as well as the potential acceptation of absence of eradication and/or unwillingness to undergo a follow-up.

Alberti proposed an individualized management algorithm for HCV patients with persistently normal ALT levels (Fig. 1) (7). In the absence of major contraindications *and* in the presence of patient motivation, immediate therapy with PEG-IFN and ribavirin should be strongly considered, particularly in patients below 45-50 years *and* infected with the easy-to-treat genotypes HCV-2/3, independently of liver histology. In patients infected with HCV-1/4 *or* patients between 50-65 years liver biopsy should be performed to decide therapy. If the liver biopsy shows F0 or F1 (Metavir score) patients should be monitored every 6 months. In the case of ≥ F2 antiviral treatment is recommended. In some patients neither biopsy nor therapy is appropriate : HCV-1/4 + high viral load + long duration of infection *or* age > 65 years *or* major contraindications. All patients with HCV infection should avoid obesity, alcohol and hepatotoxins.

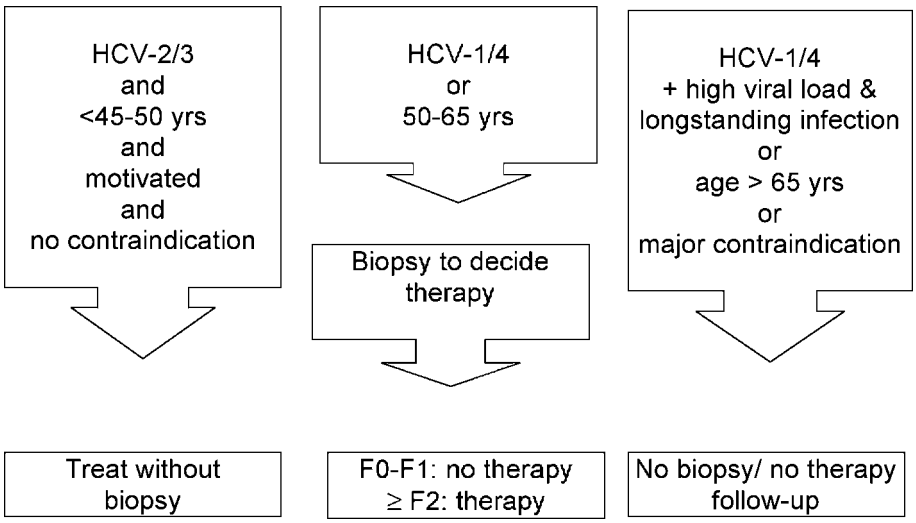

Fig. 1. — Individualized management algorithm for HCV patients with persistently normal serum ALT levels, adapted from Alberti (7).

Conclusions

Mild hepatitis C can be defined by no or mild fibrosis (Metavir F0 or F1) on liver biopsy. In addition, there should be a low risk of progression of liver fibrosis and/or no impairment in quality of life. The estimation of the risk of progression is difficult and should be based on a set of variables including age of the patient, the occurrence of ALT elevations and the role of co-factors (steatosis, alcohol intake).

Patients with mild hepatitis C should not be excluded "a priori" from the possibility of being treated, as treatment with pegylated interferon and ribavirin is safe and effective in this group. The management algorithm must take into consideration age and motivation of the patient, viral genotype, contraindications, liver biopsy and evidence of progression from mild to moderate or severe liver disease.

References

1. National Institutes of Health Consensus Development Conference Statement : Management of Hepatitis C, 10-12 June 2002. *Hepatology*, 2002, **36** : S3-20.
2. ALBERTI A., BENVEGNÙ L., BOCCATO S., FERRARI A., SEBASTIANI G. Natural history of initially mild chronic hepatitis C. *Dig. Liver Dis.*, 2004, **36** : 646-54.
3. WEISSENBORN K., KRAUSE J., BOKEMEYER M., HECKER H., SCHULER A., ENNEN J.C., AHL B., MANNS M.P., BOKER K.W. Hepatitis C virus infection affects the brain-evidence from psychometric studies and magnetic resonance spectroscopy. *J. Hepatol.*, 2004, **41** : 845-51.
4. ALBERTI A., NOVENTA F., BENVEGNÙ L., BOCCATO S., GATTA A. Prevalence of liver disease in a population of asymptomatic persons with hepatitis C virus infection. *Ann. Intern. Med.*, 2002, **137** : 961-964.
5. KIM H.C., NAM C.M., JEE S.H., HAN K.H., OH D.K., SUH I. Normal serum aminotransferase concentration and risk of mortality from liver diseases : prospective cohort study. *Br. Med. J.*, 2004, **328** : 983.
6. PRATI D., TAIOLI E., ZANELLA A., DELLA TORRE E., BUTELLI S., DE VECCHIO E., VIANELLO L., ZANUSO F., MOZZI F., MILANI S., CONTE D., COLOMBO M., SIRCHIA G. Updated definitions of healthy ranges for serum alanine aminotransferase levels. *Ann. Intern. Med.*, 2002, **137** : 1-10.
7. ALBERTI A. Towards more individualised management of hepatitis C virus patients with initially or persistently normal alanineaminotransferase levels. *J. Hepatol.*, 2005, **42** : 266-74.
8. ZEUZEM S., DIAGO M., GANE E., REDDY K.R., POCKROS P., PRATI D., SHIFFMAN M., FARCI P., GITLIN N., O'BRIEN C.B., LAMOUR F., LARDELLI P., PEGASYS Study NR16071 Investigator Group. Peginterferon alfa-2a (40 kilodaltons) and ribavirin in patients with chronic hepatitis C and normal aminotransferase levels. *Gastroenterology*, 2004, **127** : 1724-32.
9. ROSSI E., ADAMS L., PRINS A., BULSARA M., DE BOER B., GARAS G., MACQUILLAN G., SPEERS D., JEFFREY G. Validation of the FibroTest biochemical markers score in assessing liver fibrosis in hepatitis C patients. *Clin. Chem.*, 2003, **49** : 450-4.
10. CALLEWAERT N., VAN VLIERBERGHE H., VAN HECKE A., LAROY W., DELANGHE J., CONTRERAS R. Noninvasive diagnosis of liver cirrhosis using DNA sequencer-based total serum protein glycomics. *Nat. Med.*, 2004, **10** : 429-34.
11. STRADER D.B., WRIGHT T., THOMAS D.L., SEEFF L.B. Diagnosis, management and treatment of hepatitis C. *Hepatology*, 2004, **39** : 1147-1171.
12. MARCELLIN P., ASSELAH T., BOYER N. Fibrosis and disease progression in hepatitis C. *Hepatology*, 2002, **36** : S47-S56.
13. GHANY M.G., KLEINER D.E., ALTER H., DOO E., KHOKAR F., PROMRAT K., HERION D., PARK Y., LIANG T.J., HOOFNAGLE J.H. Progression of fibrosis in chronic hepatitis C. *Gastroenterology*, 2003, **124** : 97-104.
14. HUI C.K., BELAYE T., MONTEGRANDE K., WRIGHT T.L. A comparison in the progression of liver fibrosis in chronic hepatitis C between persistently normal and elevated transaminase. *J. Hepatol.*, 2003, **38** : 511-517.
15. SALOMON J.A., WEINSTEIN M.C., HAMMITT J.K., GOLDIE S.J. Cost-effectiveness of treatment for chronic hepatitis C infection in an evolving patient population. *J. Am. Med. Assoc.*, 2003, **290** : 228-237.
16. MANNS M.P., MCHUTCHISON J.G., GORDON S.C., RUSTGI V.K., SHIFFMAN M., REINDOLLAR R. GOODMAN Z.D., KOURY K., LING M., ALBRECHT J.K. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C : a randomized trial. *Lancet*, 2001, **358** : 958-965.
17. FRIED M.W., SHIFFMAN M.L., REDDY K.R., SMITH C., MARINOS G., GONCALES F.R. JR. HAUSSINGER D., DIAGO M., CAROSI G., DHUMEAUX D., CRAXI A., LIN A., HOFFMAN J., YU J. Combination of peginterferon alfa-2a plus ribavirin in patients with chronic hepatitis C virus infection. *N. Engl. J. Med.*, 2002, **347** : 975-982.
18. ANNEMANS L.,WARIE H., NECHELPUT M., PERAUX B. A health economic model to assess the long term effects and cost-effectiveness of PEG IFN β-2a in hepatitis C virus infected patients. *Acta Gastroenterol. Belg.*, 2004, **67** : 1-8.

19. MICHIELSEN P., BRENARD R., BOURGEOIS N., DE GALOCSY CH., DELWAIDE J., HENRION J., HORSMANS Y., NEVENS F., REYNAERT H., ROBAEYS G., SPRENGERS D., VAN VLIER-BERGHE H., Steering Committee Belgian Association for the Study of the Liver. Hepatitis C : screening, treatment and prevention practical guidelines. *Acta Gastroenterol. Belg.*, 2003, **66** : 15-9.

20. GRIEVE R., ROBERTS J., WRIGHT M., SWEETING M., DEANGELIS D., ROSENBERG W., BASSENDINE M., MAIN J., THOMAS H. Cost-effectiveness of interferon α or peginterferon β, with ribavirin for histologically mild chronic hepatitis C. *Gut*, 2005 (Epub June 30, 2005).