

# Current clinical care compared with new Dutch guidelines for hepatitis C treatment

S. Slavenburg<sup>1\*</sup>, M.H. Lamers<sup>1</sup>, R. Roomer<sup>2</sup>, R.J. de Knegt<sup>2</sup>, M.G.H. van Oijen<sup>1</sup>, J.P.H. Drenth<sup>1</sup>

<sup>1</sup>Departments of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands, <sup>2</sup>Departments of Gastroenterology and Hepatology, Erasmus University Medical Centre, Rotterdam, the Netherlands, \*corresponding author: tel.: +31 (0)24-361 47 60, fax: +31 (0)24-354 01 03, e-mail: S.Slavenburg@MDL.umcn.nl

## ABSTRACT

**Background:** Recently, the Dutch Association of Gastroenterology and Hepatology issued new guidelines for the treatment of chronic hepatitis C virus (HCV). These guidelines reflect the current standard of care. Before these guidelines were published and implemented we (1) studied the current clinical care of HCV patients among Dutch physicians, and (2) identified areas for future refinement in the current treatment.

**Methods:** We conducted a non-targeted survey among Dutch medical specialists in Gastroenterology, Hepatology and Internal Medicine who actively treat HCV patients. The questionnaire contained items about facility, duration and dosing of treatment, and side effect management using clinical vignettes followed by short questions.

**Results:** We received 49 questionnaires from treating HCV specialists. The majority (65%) of respondents treat HCV patients during regular outpatient clinics, while 35% treat these patients in a separate setting dedicated to the care of HCV patients. The majority of physicians follow the stipulated dosage regimens of pegylated interferon (88%) and ribavirin (83%). A minority (13%) exceed the advised dosage of ribavirin. Side effects such as neutropenia are mostly managed by decreasing the interferon dosage (42%). Some 35% of physicians reduce ribavirin if haemoglobin levels drop below 5.4 mmol/l, and 41% initiate erythropoietin treatment.

**Conclusion:** Dutch clinical practice reflects the recently issued HCV guidelines. An important area of refinement in treatment of HCV is the management of side effects.

## KEYWORDS

Current practice, guidelines, hepatitis C, survey

## INTRODUCTION

Chronic hepatitis C virus (HCV) is one of the most common chronic viral infections throughout the world and is a primary cause of cirrhosis and hepatocellular carcinoma.<sup>1</sup> Treatment of HCV has improved steadily during the last decade, and with the current standard of care, that is treatment with pegylated interferon and ribavirin, sustained virological response (SVR) rates of 50% among genotypes 1 and 4, and 80% among genotypes 2 and 3 have become possible.<sup>2,3</sup>

The selection of patients who benefit most from therapy and close monitoring of hepatitis C treatment are crucial components of hepatitis C therapy. These aspects, and the wealth of clinical data that stem from a large number of clinical trials, have led to the formulation of international guidelines.<sup>4,5</sup> Given the intensive treatment schedule with side effects, long treatment duration and high costs of therapy, it is important that physicians follow evidence-based guidelines in order to improve patient outcome and give the best care available.<sup>4,5</sup> Recently, the first Dutch national guideline 'Treatment of chronic hepatitis C virus infection' was formulated by the Dutch Association of Gastroenterologists and Hepatologists.<sup>6</sup> This guideline for HCV mono-infection provides recommendations on diagnostic evaluation, choice of the (initial) antiviral treatment and the follow-up during and after antiviral therapy (table 1, figure 1).<sup>6</sup>

Although clinical trials have demonstrated the benefit of combination therapy in patients with chronic HCV, how this translates into actual benefit in practice that can be attributed to knowledge of and adherence to guidelines is unclear. The primary objective of this study was to evaluate current clinical practice among Dutch physicians who actively see and treat chronic HCV patients. A secondary objective was to identify dimensions of the guideline that potentially benefit from refinement or adjustment.

**Table 1.** Main recommendations for treatment and management of chronic HCV patients<sup>6</sup>

	Dutch guideline <sup>6</sup>	% followed guideline*
<b>Dosage</b>		
HCV genotype 1 and 4	Peg-IFN $\alpha$ -2a 180 $\mu$ g/week + weight-based RBV/day or Peg-IFN $\alpha$ -2b 1.5 $\mu$ g/kg/week + weight-based RBV/day	83%
HCV genotype 2 and 3	Peg-IFN $\alpha$ -2a 180 $\mu$ g/week + 800 mg RBV/day or Peg-IFN $\alpha$ -2b 1.5 $\mu$ g/kg/week + weight-based RBV/day	88%
<b>Duration</b>		
HCV genotype 1 and 4	48 weeks of treatment Exception: <600,000 viral load (IU/ml) at baseline with RVR: 24 weeks of treatment	67% 55%
HCV genotype 2 and 3	24 weeks of treatment Exception: with RVR: 12-16 weeks of treatment	70% -
<b>Side effects</b>		
Neutropenia	ANC <0.75 x 10 <sup>9</sup> /l: PEG-IFN dose to 75% ANC <0.375 x 10 <sup>9</sup> /l: PEG-IFN dose to 50%	35% -
Anaemia	Hb <5.0 mmol/l: give erythropoietin Hb <4.0 mmol/l: decrease dose RBV to 800 mg/day and give erythropoietin and blood transfusion	25% -
HCV = hepatitis C virus; Peg-IFN = peginterferon; RBV = ribavirin; RVR = rapid viral response; ANC = absolute neutrophil count; Hb = haemoglobin. *% physicians who treat according to the Dutch guideline.		

## METHODS

We conducted a non-targeted survey among Dutch medical specialists in Gastroenterology, Hepatology and Internal Medicine. These physicians were selected from membership directories of the Dutch Society of Hepatology and the Infectious Disease Society of the Netherlands and were sent a postal questionnaire; physicians who actively treated HCV patients were asked to return the questionnaire.

The postal questionnaire included four important issues: the first part discussed the setting of the treatment: a regular outpatient clinic or a separate setting dedicated to the care of HCV patients. The second and third part of the survey focused on peginterferon and ribavirin treatment for HCV patients: detailed questions using clinical vignettes were included about the treatment duration and dosage of the drugs, respectively. The last part focused on side effects, their consequences, and management in terms of dose reduction or treatment of possible side effects.

The questionnaire consisted of clinical vignettes followed by a mix of short multiple-choice and open-ended questions. For example: 'A male HCV genotype 1 patient starts the combination therapy (peginterferon 180  $\mu$ g/week and weight-based ribavirin daily); at the start of the treatment the haemoglobin (Hb) level is 8.0 mmol/l. After eight weeks the patient's Hb has decreased to 5.4 mmol/l. What to do? 1) Continue combination therapy. 2) Stop ribavirin (whether or not temporarily). 3) Reduce ribavirin to 50%. 4) Give erythropoietin. 5) Give blood transfusion.' Data from returned questionnaires were entered into a Microsoft Access database, and frequency tables were provided by SPSS 14.0 for Windows.

## RESULTS

A total of 64 questionnaires were received. Although explicitly indicated, 15 responding specialists were not actively treating HCV patients and were excluded from further analysis. Forty-nine questionnaires were suitable for analysis.

### Setting

The majority (65%) of respondents treat HCV patients during regular outpatient clinics, while 35% treat patients in a separate setting dedicated to the care of HCV patients.

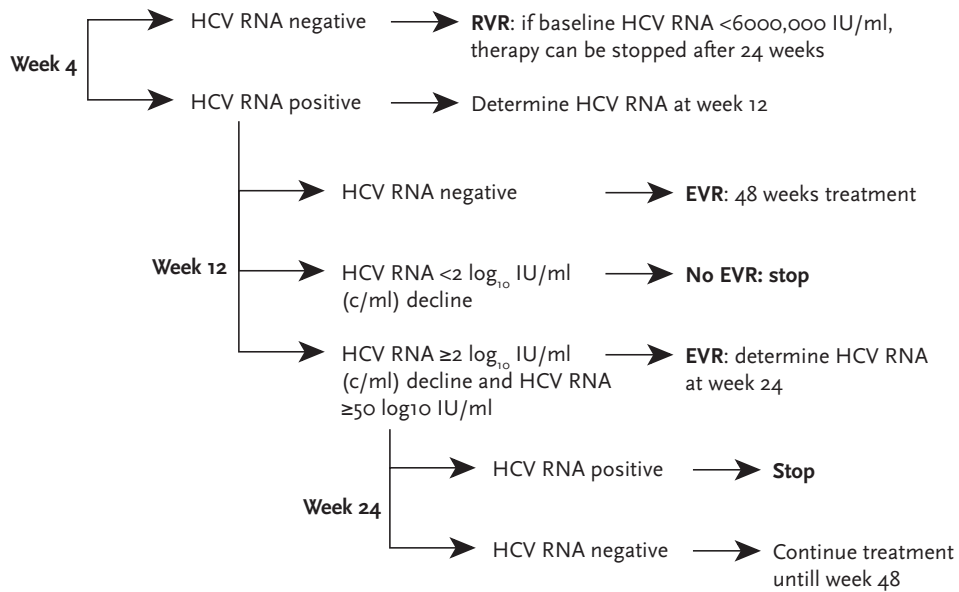
### Viral load, genotype and length of treatment

Week 12 and 24 measurements of viral load are important to judge treatment outcome. When asked, 67% of physicians would treat HCV genotype 1 patients with a detectable HCV viral load at week 12 and an undetectable HCV viral load at 24 weeks for a total of 48 weeks (table 1), while 13 of the 49 respondents (27%) choose longer treatment (72 weeks). This is an area of controversy since the guideline indicates 48 weeks, but recent evidence suggests that prolonged treatment up to 72 weeks is beneficial in these cases.<sup>7,8</sup>

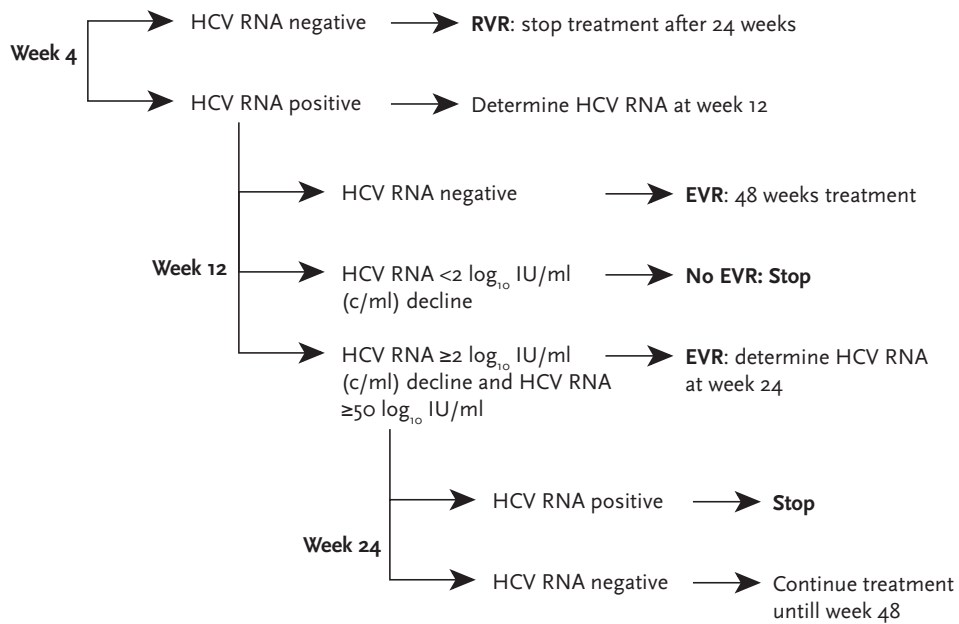
The guideline recommends treating HCV genotype 3 patients for 24 weeks. Some 70% of respondents treat HCV genotype 3 patients with significant cirrhosis for 24 weeks, while a minority (22%) will treat for 48 weeks. For HCV genotype 3 patients who had a negative viral load at week 4, the guideline recommends treating for 12 to 16 weeks. Thirty-seven percent of the respondents would treat for this period. The remainder choose a longer treatment duration than currently advised in the guideline.

**Figure 1.** Flowchart for the treatment of patients with chronic hepatitis C mono-infection according to the recently issued Dutch guideline<sup>6</sup>

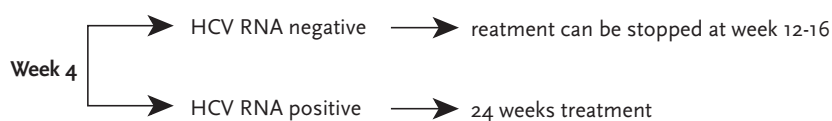
**A) HCV genotype 1**



**B) HCV genotype 4**



**C) HCV genotype 2 and 3**



Respondents were also divided on treatment duration of genotype 1 patients with low viraemia (<600,000 IU/ml) at the start of treatment, and a negative viral load at week 4. While following the guideline, some 55% would treat for 24 weeks, and 45% would treat for 48 weeks.

### Ribavirin

The recommended dosage of ribavirin for HCV genotype 1 patients is weight-based. Indeed, the majority of physicians treat an HCV genotype 1 patient with a weight of 104 kg with ribavirin on a weight-based schedule (83%). A minority (13%) consistently exceeds this dosage.

### Peginterferon

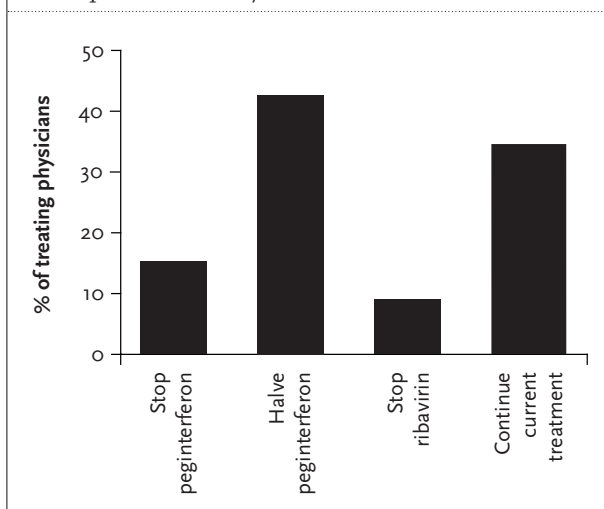
The vignette on the peginterferon dosage in an HCV genotype 1 patient weighing 150 kg shows that 88% of the physicians administer the dosage exactly as stated in the guideline. Thus, peginterferon- $\alpha$ -2a, 180  $\mu$ g/week, or weight-based peginterferon- $\alpha$ -2b, 1.5  $\mu$ g/week. The remainder choose a higher dosage than currently advised in the guideline.

### Side effect management

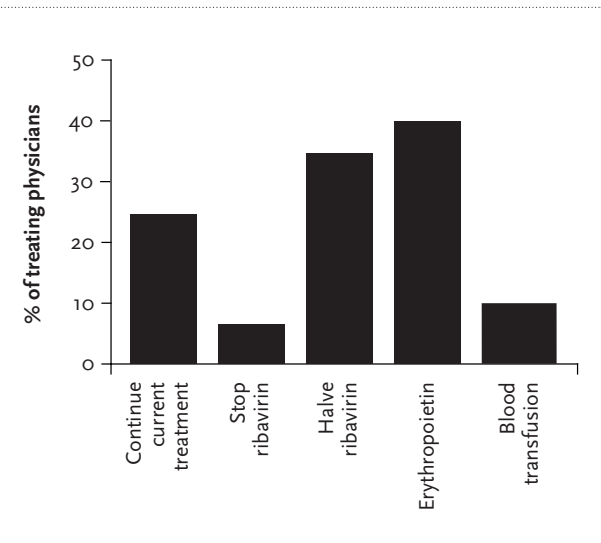
Neutropenia is a common event in HCV combination therapy and is usually attributed to the peginterferon component. Upon managing a patient with profound neutropenia ( $0.8 \times 10^9/l$ ), 35% would continue current treatment, 42% would reduce (halve) the prescribed dosage of peginterferon, and 15% stop peginterferon (figure 2).

Anaemia is caused by ribavirin-induced haemolysis, and if asked to decide for a patient with haemoglobin <5.4 mmol, the majority of physicians (41%) would initiate erythropoietin treatment, while 35% of physicians would reduce the ribavirin. Twenty-five percent continue both pegylated interferon and ribavirin unchanged (figure 3).

**Figure 2.** Management choices in treatment of neutropenia  $0.8 \times 10^9/l$



**Figure 3.** Management choices in treatment of haemoglobin levels below 5.4 mmol/l



### DISCUSSION

Our survey shows that most physicians treat patients with HCV in clinical practice according to this recently issued HCV guideline.

Still there are some areas of controversy. Almost half of the physicians treat HCV genotype 1 and 3 patients with RVR longer than currently needed. In terms of financial aspects, occurrence of severe side effects and convenience for patients, shorter treatment duration with retained efficacy is desirable.

Some 13% of the physicians use higher ribavirin dosages than currently advised. Some studies show that a higher starting dose of ribavirin is associated with a lower relapse rate and higher rate of SVR.<sup>9-11</sup> High-dose ribavirin is also associated with more frequent and serious side effects such as anaemia, which require erythropoietin in many cases.<sup>9-11</sup> More studies are necessary to judge whether the benefits of a higher ribavirin dosage needed to achieve SVR outweigh the disadvantages of the side effects.<sup>12</sup>

Management of side effects has low evidential value and the current literature is mostly based on expert opinion. When a side effect, e.g. neutropenia or anaemia, occurs peginterferon and ribavirin are often reduced or stopped too soon,<sup>13</sup> and this may hamper the achievement of SVR. On the other hand, if treatment of anaemia by erythropoietin is initiated too early, it leads to unnecessary expenses.<sup>9,14</sup> Supporting evidence in order to issue guidelines is clearly needed. Along the same line, neutropenia due to peginterferon can be controlled by granulocyte colony stimulating factor, but it is unclear which cut-off point should be used for initiating therapy.

This study has some limitations. We did not ask for respondents' demographics, professional background and/or hospital setting. It is unclear whether our findings are generalisable to all Dutch medical specialists in Gastroenterology, Hepatology and Internal Medicine. Altogether, data from our survey indicate that Dutch physicians treat their HCV patients as described in the recently issued HCV treatment guideline. There is a paucity of data that enables evidence-based management of side effects during HCV therapy.

## REFERENCES

1. Strader DB, Wright T, Thomas DL, Seeff LB. American Association for the Study of Liver Diseases: diagnosis, management, and treatment of hepatitis C. *Hepatology*. 2004;39:1147-71.
2. Manns MP, McHutchison JG, Gordon SC. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet*. 2001;358:958-65.
3. Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med*. 2002;347:975-82.
4. Asian Pacific Association for the Study of the Liver (APASL) Hepatitis C Working Party. Asian Pacific Association for the Study of the Liver consensus statements of the diagnosis, management and treatment of hepatitis C virus infection. *J Gastroenterol Hepatol*. 2007;22:615-33.
5. Consensus conference. Treatment of hepatitis C. *Gastroenterol Clin Biol*. 2002;65:115-7.
6. De Bruijne J, Buster EH, Gelderblom HC, et al. Treatment of chronic hepatitis C virus infection – Dutch national guidelines. *Neth J Med*. 2008;66:49-60.
7. Sánchez-Tapias JM, Diago M, Escartin P, et al. Peginterferon-alfa2a plus ribavirin for 48 versus 72 weeks in patients with detectable hepatitis C virus RNA at week 4 of treatment. *Gastroenterology*. 2006;131:451-60.
8. Berg T, von Wagner M, Nasser S, et al. Extended treatment duration for hepatitis C virus type 1: comparing 48 versus 72 weeks of peginterferon-alfa-2a plus ribavirin. *Gastroenterology*. 2006;130:1086-97.
9. Shiffman ML, Salvatore J, Hubbard S, et al. Treatment of Chronic Hepatitis C Virus Genotype 1 with Peginterferon, Ribavirin, and Epoetin alpha. *Hepatology*. 2007;46:371-9.
10. Lindahl K, Stahle L, Bruchfeld A, Schvarz R. High-dose ribavirin in combination with standard dose peginterferon for treatment of patients with chronic hepatitis C. *Hepatology*. 2005;41:275-9.
11. Jacobson IM, Brown R, Freilich B, et al. Weight-based ribavirin dosing increases sustained viral response in patients with chronic hepatitis C: final results of the WIN-R study, A US community based trial [Abstract]. *Hepatology*. 2005;42(suppl 1):749A.
12. Bergmann CJF, Slavenburg S, Roomer R, de Knegt RJ, Drenth JPH. Rationale and design of the virological response and ribavirin dosage (VIRID) study in hepatitis. *Neth J Med*. 2008;65:44-5.
13. Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 3.0, DCTD, NCI, NIH, DHHS; March 31, 2003. <http://ctep.cancer.gov>, 9 August 2006.
14. Bezemer G, Schalm SW, van Gool AR, de Knegt RJ. Wijzigingen in het beleid bij patiënten met bijwerkingen van de behandeling van hepatitis C. *Ned Tijdschr Geneesk*. 2007;151:525-30.