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SPECIAL REPORT

Treatment of chronic hepatitis C virus infection – Dutch national guidelines

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ABSTRACT

The development of this guideline was initiated and coordinated by the Netherlands Association of Gastroenterologists and Hepatologists (Nederlandse Vereniging van Maag-Darm-Leverartsen). The aim is the establishment of practical guidelines in the evaluation and antiviral treatment of patients with chronic hepatitis C virus (HCV) infection. This includes recommendations for the initial evaluation of patients, the choice and duration of antiviral therapy and the follow-up after antiviral therapy.

Hepatitis C is a slowly progressive disease. The initial evaluation of chronically HCV-infected patients should include liver biochemistry testing, virological testing and abdominal ultrasound imaging. Liver biopsy is no longer a routine procedure.

Antiviral treatment should be considered for all HCV-infected patients. Current antiviral treatment is a long-term process and is associated with substantial side effects. When deciding whether to start treatment or not, the chance of successful treatment (80% with hepatitis C genotype 2 and 3 and 50% with hepatitis C genotype 1 and 4), the fibrosis stage, the expected side effects and the compliance of the patient should be taken into consideration. In the absence of significant fibrosis and necroinflammation in liver biopsy, postponing treatment is an option. Current antiviral treatment is contraindicated in patients with Child-Pugh-class B or C cirrhosis. The possibility of a liver transplantation should be investigated in these patients. Significant comorbidity with a limited life expectancy is an absolute contraindication for antiviral treatment.

Treatment of chronic hepatitis C consists of administration of peginterferon and ribavirin for 24 or 48 weeks. Patients with hepatitis C genotype 1 or 4 are treated for 48 weeks. Patients with hepatitis C genotype 2 or 3 are treated for 24 weeks. In patients with undetectable HCV RNA after four weeks (28 days) of treatment, a shorter treatment is equally effective (12 to 16 weeks for hepatitis C genotype 2 or 3; 24 weeks for hepatitis C genotype 1 or 4). Outpatient clinic visits are recommended at the start and after 2, 4, 8, and 12 weeks of treatment, and thereafter every four to six weeks until the end of treatment. It is recommended to stop treatment if the HCV RNA level has not decreased by at least 2 $\log_{10}$ IU/ml (c/ml) after 12 weeks of treatment or when HCV RNA is still detectable after 24 weeks of treatment.

The recommended frequency of outpatient clinic visits for patients who are not being treated is once every six months in patients with cirrhosis, otherwise every 12 months.

It is expected that new anti-HCV-medication (STAT-C, specifically targeted antiviral therapy for HCV) will become available in the near future. Therefore treatment of chronic HCV infection will probably be more effective in the future.

INTRODUCTION

Over 130 million people suffer from chronic hepatitis C virus infection (HCV infection) worldwide.[1-3] In the Netherlands the number of people with chronic HCV infection is estimated to be 60,000.[4] (Estimated

seroprevalence of anti-HCV in the Netherlands is 0.5%, 75% of the people with anti-HCV are viraemic). HCV is an RNA virus that belongs to the family of the *Flaviviridae*. The main route of transmission is parenteral via contaminated blood (blood transfusion, re-use of inadequately sterilised instruments, intravenous drug use). Sexual transmission is rare. Six HCV genotypes exist, of which the genotypes 1, 2, 3 and 4 are prevalent in the Netherlands. Hepatitis C is a slowly progressive disease which initially causes no or few symptoms in most HCV-infected patients. Approximately 10 to 20% of HCV-infected patients develop cirrhosis over a period of 10 to 30 years. Per year, 1 to 5% of patients with cirrhosis develop hepatocellular carcinoma (HCC). Cirrhosis and HCC as a result of chronic HCV infection are currently the major indications for liver transplantation in Europe and the United States.[5] Liver transplantation is an effective treatment for decompensated cirrhosis (Child-Pugh class B or C) and for small HCCs.[6] However, the transplanted donor liver will be re-infected with HCV. As a result 10 to 41% of the patients will develop cirrhosis of the donor liver after five to ten years.[5,7]

No vaccine or immunoglobulin is available for the prevention of HCV infection. The main groups at risk for HCV infection are persons who have ever used intravenous drugs, recipients of blood or blood products before 1992 and immigrants from high endemic areas. Chronic HCV infection can be treated with combination therapy consisting of peginterferon-α (a cytokine) and ribavirin (a nucleoside analogue) for 24 to 48 weeks. The duration of the treatment depends on the HCV genotype, the quantity of HCV in plasma at the start of treatment and the viral decline during treatment.

Multiple consensus guidelines for the treatment of chronic hepatitis C have been published in the last few years.[8,9] A committee was convened by the Netherlands Association of Gastroenterologists and Hepatologists (Nederlandse Vereniging van Maag-Darm-Leverartsen) to formulate a consensus-based guideline for the treatment of chronic HCV infection. The guideline provides recommendations on the initial evaluation of chronically HCV-infected adults, choice of the (initial) antiviral therapy and the follow-up during and after antiviral therapy. Management of patients with co-infection of hepatitis B virus (HBV) and hepatitis C virus (HCV) or human immunodeficiency virus (HIV) will not be discussed in this guideline. This guideline will only discuss the treatment with pegylated interferon-α and ribavirin. The level of recommendation was determined according to the Dutch Institute for Quality of Healthcare (CBO) (http://www.cbo.nl/product/ richtlijnen/ handleiding_ebro/article20060207153532) *(tables 1A and 1B)*.

Table 1A. *Quality of studies on which a recommendation is based*

Grade	Definition
A1	Systematic review of at least two independent studies of A2 level
A2	Randomised double-blind controlled study of adequate quality and size
B	Comparative study not fulfilling the characteristics of A2 level studies (including case-control studies and cohort studies)
C	Noncomparative studies
D	Expert opinion

Table 1B. *Quality of evidence on which a recommendation is based*

Grade	Definition
I	Study of level A1 or at least two independent studies of level A2
II	Single level A2 study or at least two independent level B studies
III	Single level B or C study
IV	Expert opinion

NATURAL HISTORY

Acute hepatitis C virus infection is rarely observed. The course of HCV infection is usually asymptomatic;[10-12] fulminant hepatitis is rare.[13] HCV RNA is first detectable seven to ten days after exposure,[14,15] HCV-specific antibodies are detectable after 49 to 70 days.[16,17] About 75% of HCV-infected patients develop chronic infection and in 25% the infection resolves spontaneously.[18-21] In patients with a suspected acute HCV infection (for example after needlestick injury with an HCV RNA-positive source) it is recommended to determine the HCV RNA load regularly and to start treatment if viraemia develops within 12 weeks after exposure.[10,22] Studies have shown that the chance of achieving a sustained viral response is 90 to 100% after treatment with interferon or peginterferon monotherapy for 24 weeks, independent of the genotype.[10,22]

Chronic HCV infection is defined by the presence of HCV RNA for more than six months. The grade of hepatitis can vary from minimal inflammation to serious inflammatory activity with fibrosis or cirrhosis. The course of the infection is independent of the level of the enzyme alanine aminotransferase (ALAT) in plasma. Fibrosis and cirrhosis can emerge despite normal levels of ALAT. After 10 to 30 years, 10 to 20% of the patients develop cirrhosis. Progression of the disease is slower in females and in those who are young at the time of infection, but faster in patients with a high inflammatory activity, alcohol consumption, or co-infection with HBV or HIV.[23] In patients with cirrhosis, the incidence of HCC is 1 to 5% per year. Death of patients with chronic HCV infection and

cirrhosis can occur due to decompensation of the cirrhosis or to development of HCC.[2,3,24-26] The incidence of HCC and the mortality due to HCV will probably increase in the coming decades.[27,28]

Cohort studies (retrospective – prospective) show that after 25 to 35 years, 5 to 12% of the infected patients will develop decompensated cirrhosis or HCC.[29-31] Few studies have investigated the natural course of chronic HCV infection.[25,26,32] Studying the natural course of chronic HCV infection is difficult because the majority of hepatitis C infected patients have not yet been identified. Many HCV-infected individuals are unaware of their infectious status and do not have symptoms. Chronic HCV infection is a disease with nonspecific symptoms, such as fatigue. It often is diagnosed accidentally. Some extrahepatic manifestations, such as lichen planus, Sjögren's syndrome and vasculitis on the basis of cryoglobulinaemia are associated with chronic HCV infection.[33,34]

It is not clear whether the route of transmission influences the course of disease. Among young intravenous drug users with chronic HCV infection the mortality rate is higher due to complications related to the intravenous drug use as compared with liver disease related to the hepatitis C virus infection.[35]

Although death as a result of end-stage liver disease due to chronic HCV infection occurs in probably less than 30% of all HCV-infected patients,[36] the worldwide epidemic leads to a mortality rate of approximately 350,000 deaths per year. This number will probably increase in the coming years.[37]

INITIAL EVALUATION

The initial evaluation of patients with chronic HCV infection should include a detailed history, with special emphasis on risk factors for blood-borne infectious diseases and alcohol abuse. Physical examination should focus on signs of chronic liver disease and cirrhosis (palmar erythema, spider nevi, gynaecomastia, flapping tremor and testicular atrophy), portal hypertension (ascites, splenomegaly, caput medusae) and liver failure (jaundice and hepatic encephalopathy).

Laboratory tests should include assessment of liver enzymes (aminotransferases), liver function tests (albumin, bilirubin and prothrombin time), full blood cell count and kidney function tests. The replication status (quantitative HCV RNA) and the HCV genotype should be determined when antiviral treatment is considered. In addition, the patient must be tested for HBV or HIV co-infection. Abdominal ultrasound should be performed in all patients, with special emphasis on signs of cirrhosis (irregular liver surface, blunt liver edge and narrowed hepatic veins), portal hypertension (diminished portal flow, splenomegaly, venous collaterals and ascites) and focal liver lesions.

Liver biopsy does not have to be routinely performed in all HCV-infected patients. A liver biopsy could be considered for assessing the need for antiviral treatment, to assess baseline necroinflammatory activity and fibrosis stage *(table 2)*. In patients with genotype 2 or 3, with successful treatment rates of 80% or more, liver biopsy often has no added value.

Table 2. *Recommendations for the management of chronic hepatitis C based on fibrosis stage and presence of (decompensated) cirrhosis*

Fibrosis/cirrhosis	Recommended management
None	Antiviral therapy is not strictly indicated, yearly monitoring
Moderate	Antiviral therapy is indicated
Compensated cirrhosis	Antiviral therapy is indicated, 6-monthly monitoring
Decompensated cirrhosis	Liver transplantation indication, monitor more than twice a year

Specific tests prior to treatment should include autoantibodies (antinuclear antibodies, ANA) and thyroid stimulating hormone. A chest X-ray (in case of pulmonary symptoms, older age, to rule out sarcoidosis and tuberculosis) and an electrocardiogram (ECG) (in case of cardiac symptoms, older age) should be performed on indication *(table 3)*. Patients with diabetes mellitus or pre-existing eye disease should undergo fundoscopy. A pregnancy test should be carried out in fertile females. Females should not become pregnant during ribavirin treatment or within four months after ribavirin treatment has been stopped.[38-41] Males should not cause pregnancy during ribavirin treatment or within seven months after ribavirin treatment has been stopped.[38-41] Due to the long half-life of ribavirin it takes eight to ten weeks before ribavirin is eliminated from the body. If pregnancy occurs during or just after ribavirin treatment is stopped, the possibilities of side effects on the foetus should be discussed; however it should be noted that the risk of foetal abnormalities is regarded to be small. In the literature pregnancies have been described during or just after the use of ribavirin; none of these pregnancies have led to congenital disorders.[42-46] The outcomes of such pregnancies are registered (www.ribavirinpregnancyregistry.com) in an international database. As a precaution, the American Food and Drug Administration (FDA) classified ribavirin in the FDA Pregnancy category X.[47]

Surveillance for HCC, by abdominal ultrasound every six to 12 months, is recommended for all chronically HCV-infected patients with cirrhosis.[48,49] Screening for HCC results in the detection of HCC in an earlier stage and is associated with better survival rates.[50] Routine measurement of α-fetoprotein is not useful as this does not improve the efficacy of screening and leads to an increase in false-positive findings.[48] In patients with cirrhosis,

Table 3. *Recommendations for minimal laboratory testing prior to, at start and during antiviral therapy with peginterferon and ribavirin*

	Prior	At start	W1	W2	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48
Routine laboratory	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Screening	X															
Endocrinology	X						X			X			X			X
Level of HCV RNA		X			X		X			X						X
Radiology	X															X
ECG	X															
Pregnancy test	X															

Routine laboratory	Haemoglobin, leucocytes with differential WBC, thrombocytes, ALAT, ASAT, alkaline phosphatase, gamma-GT, LDH, glucose, HbA_{1C} if glucose is elevated (routine assessment of glucose and leucocyte differentiation only during treatment)
Screening	PT, APT, AT III, albumin, creatinine, antinuclear antibodies, HBsAg, anti-HBs, anti-HBc, anti-HIV
Endocrinology	TSH, and when elevated FT4
Level of HCV RNA	HCV RNA-concentration quantitative and/or qualitative
Quantitative	Prior to treatment, preferably just before the first peginterferon injection and at week 4 and week 12
Qualitative	After 4, 12, 24 en 48 weeks of treatment, and 24 weeks after stopping treatment
Radiology	Abdominal ultrasound of liver and spleen, including Doppler ultrasound test, chest X-ray on indication
ECG	On indication
Pregnancy test	Only in females in the age of procreation

upper gastrointestinal endoscopy should be considered to confirm or exclude the presence of oesophageal varices.
Hepatitis A virus (HAV) immunity should be established in all patients with chronic hepatitis C, since the risk of a fulminant course of acute HAV infection is increased as compared with healthy controls.[51] Despite the fact that the actual risk of fulminant HAV infection is low, HAV vaccination is recommended for all chronically HCV-infected patients not immune to HAV infection.
Co-infection with HBV can accelerate the progression of chronic HCV infection.[52] Therefore, HBV vaccination is recommended in all patients with chronic HCV infection without protective HBV immunity.[8,51,52]

Recommendations	
The initial evaluation of chronically HCV-infected patients should include a detailed history and physical examination. Blood chemistry, full blood cell count, virus serology (including determination of the HCV genotype and quantification of plasma HCV RNA) and abdominal ultrasound should also be performed.	Level 4
Surveillance for hepatocellular carcinoma by abdominal ultrasound every 6 to 12 months is recommended in patients with cirrhosis.	Level 3
Hepatitis A vaccination is recommended in all chronically infected hepatitis C patients without hepatitis A immunity because of the increased risk of developing fulminant acute hepatitis A virus infection.	Level 1
Co-infection with hepatitis B virus can accelerate the disease progression. Therefore, hepatitis B vaccination is recommended in all chronically HCV-infected patients without protective immunity to hepatitis B.	Level 1

INDICATIONS AND CONTRAINDICATIONS FOR ANTIVIRAL THERAPY

Antiviral treatment should be considered in all chronically HCV-infected patients. Current antiviral treatment is a long-term process and is accompanied with a number of side effects. When deciding whether or not to start treatment, the chance of successful treatment (80% with hepatitis C genotype 2 and 3 after 12 to 24 weeks treatment, 50% with hepatitis C genotype 1 and 4 after 24 to 48 weeks treatment), the fibrosis stage, the expected side effects and the motivation of the patient should be taken into consideration. In the absence of fibrosis and inflammation in the liver biopsy, postponing treatment can be considered.
Contraindications for antiviral treatment are the presence of Child-Pugh-class B or C cirrhosis or significant comorbidity (severe cardiac disease, chronic obstructive pulmonary disease (COPD), systemic lupus erythematosus (SLE), other autoimmune diseases or severe psychiatric disorders). Relative contraindications are age of 70 years or above, mild comorbidity and various social factors. In patients with pre-existing comorbidity such as depression, COPD, psoriasis, diabetes mellitus, one should be alert for exacerbations of these diseases during antiviral therapy. It is recommended to consult other specialists (psychiatrist, pulmonologist, dermatologist, internist, ophthalmologist) before starting antiviral therapy and take precautionary measures if necessary (for example to start treatment with a selective serotonin reuptake inhibitor (SSRI) in a patient with a history of depression).[53] When relative contraindications are present, the stage of the liver

disease, the HCV genotype and the chance of achieving a sustained viral response (SVR), the expected duration of antiviral therapy and other factors associated with response have to be taken into account as well. Important factors predisposing for nonresponse are age above 40 years, male gender, negroid race,[54,55] obesity[56] and high γ-GT levels.[57,58] If the indications for treatment are not clear or contraindications exist, it is recommended to consult an expertise centre.

Recommendations	
Antiviral treatment should be considered in all chronically HCV-infected patients.	Level 4
Considering whether or not to start treatment, the chance of successful treatment (80% with hepatitis C genotype 2 and 3 after 12 to 24 weeks treatment, 50% with hepatitis C genotype 1 and 4 after 24 to 48 weeks treatment), the fibrosis stage, the expected side effects and the compliance of the patient should be taken into account. In the absence of fibrosis and inflammation in the liver biopsy, postponing antiviral treatment can be considered.	Level 1

MONITORING PATIENTS NOT REQUIRING ANTIVIRAL THERAPY

Patients without indication for antiviral therapy, patients with contraindications for antiviral therapy (COPD, diabetes mellitus with organ injury, etc), patients who do not want to be treated and patients who did not achieve an SVR after antiviral therapy (nonresponse, breakthrough, relapse) should be monitored by a hepatologist. These patients should be monitored yearly for routine assessment of blood tests (ALAT, ASAT, albumin, bilirubin, PT, full blood cell count). Abdominal ultrasound should be considered every three to five years. Patients with cirrhosis should be monitored every six months, including abdominal ultrasound.

Nonresponders, relapsers, patients with breakthrough and other difficult to treat patients

Approximately 20% (genotype 2 and 3) to 50% (genotype 1 and 4) of patients do not respond to current standard peginterferon and ribavirin therapy. Three types of non-SVR can be distinguished: nonresponse, breakthrough and relapse *(table 4)*. The most important viral factor associated with non-SVR is genotype 1 or 4. A number of studies showed that an initial high viral load is associated with a lower chance of achieving an SVR.[9] The SVR rate after retreatment with standard therapy is usually low (less than 25%). Retreatment of non-SVR patients should preferentially be done in an investigational setting. Patients with non-SVR after IFN monotherapy have a slightly higher chance of achieving an SVR after retreatment with peginterferon and ribavirin as compared with retreatment of patients with non-SVR after combination therapy with peginterferon and ribavirin. Also patients with extensive comorbidity, such as end-stage kidney failure with or without haemodialysis, status after transplantation, autoimmune disease (SLE) are considered difficult to treat. Patients with non-SVR and other difficult to treat patients can be referred to an expertise centre for retreatment, preferably in an investigational setting.

Table 4. *Antiviral therapy outcomes*

Treatment outcome		HCV RNA
SVR		Undetectable HCV RNA with qualitative PCR-test 24 weeks after end of antiviral therapy
Non-SVR	Nonresponse	Detectable HCV RNA with qualitative PCR-test during and at end of antiviral therapy
	Breakthrough	Detectable HCV RNA at any time during treatment after previous undetectable HCV RNA with qualitative PCR-test during antiviral therapy
	Relapse	Undetectable HCV RNA with qualitative PCR-test at end of treatment, but detectable 24 weeks after stopping antiviral therapy

SVR = sustained viral response.

Recommendation	
Every chronically HCV-infected patient not receiving antiviral therapy should be monitored at least once yearly for the routine assessment of blood tests. Patients with cirrhosis should be monitored every 6 months.	Level 4

ANTIVIRAL THERAPY

The current standard antiviral therapy for chronic HCV infection consists of administration of peginterferon and ribavirin for 24 or 48 weeks.[59-62] Peginterferon is administered subcutaneously once a week and ribavirin should be taken orally twice daily. The goal of antiviral therapy is to achieve an SVR, thereby resolving liver inflammation and the progression to cirrhosis and HCC.[63]

In patients with genotype 1, treatment with peginterferon and ribavirin results in an SVR in 41 to 52% of the patients after 48 weeks of treatment[59-61,64] and in patients with genotype 4 in 77%.[59] In patients with genotype 1, the SVR rate after a shorter treatment of 24 weeks is diminished to 29 to 42%.[60,64] In patients with genotype 2 and 3, treatment for 24 weeks (79 to 93%) results in an equal SVR rate as compared with 48 weeks of treatment (76 to 88%).[59-61,64,65] The duration of antiviral therapy is dependent on the genotype and the

Table 5. *Recommendations for evaluation of the viral response during treatment*

Time point	Response	HCV RNA	Clinical meaning
Week 4	Rapid viral response (RVR)	Undetectable with qualitative PCR-test	RVR results in a better chance of an SVR, possibility of shorter treatment
Week 12	Early viral response (EVR)	> 2 $\log_{10}$ IU/ml (c/ml) decline compared with start of therapy	If EVR is not achieved, the chance of an SVR is nil, stop treatment

HCV RNA load at the start of therapy and during treatment (*table 5*).[8,62,66] Antiviral therapy with peginterferon and ribavirin is costly and most patients suffer from significant side effects (*table 6*).[9,67,68]

There are two types of peginterferon, which have comparable efficacy in clinical practice. The dose of peginterferon-α-2b is weight-based: 1.5 µg/kg/week, the dose of peginterferon-α-2a is always 180 µg/week.[69] Recent studies suggest that weight-based dosing of ribavirin is associated with a higher chance of achieving an SVR.[70,71] However, these studies were performed exclusively with peginterferon α-2b.

Table 6. *Side effects during treatment with peginterferon and ribavirin*[22,67,68]

Frequency	Peginterferon	Ribavirin
>30% (very frequent)	Flu-like symptoms Headache Fatigue Pyrexia Chills Myalgia Thrombocytopenia Induction of autoantibodies	Haemolysis Nausea
1-30% (frequent)	Anorexia Erythema at injection site Insomnia Alopecia Lack of motivation Lack of concentration Irritability, agitation Emotional instability Depression Diarrhoea Autoimmune disease (thyreoiditis, Sjögren's disease) Neutropenia Change of taste	Anaemia Obstructed nose Pruritus Diarrhoea Eczema
<1% (rare)	Polyneuropathy Paranoia of suicidal ideation Diabetes mellitus Retinopathy Optic neuritis Hearing loss Seizures Loss of libido Cardiotoxicity	Gout Interstitial pneumonia

Antiviral therapy of HCV genotype 1

The treatment of HCV genotype 1 consists of the administration of peginterferon-α-2a 180 µg/week in combination with weight-based ribavirin daily (1000 mg for <75 kg, 1200 mg for ≥75 kg) or peginterferon-α-2b at a weekly dose of 1.5 µg/kg in combination with weight-based ribavirin (800 mg from ≤65 kg, 1000 mg from 65 to 85 kg, 1200 mg from 85 to 105 kg and 1400 mg from ≥105 kg) (*tables 7* and *8*). The duration of antiviral therapy is 48 weeks. After 12 weeks of antiviral therapy HCV RNA should be tested to determine the viral response. If the HCV RNA level after 12 weeks has decreased less than 2 $\log_{10}$ IU/ml (c/ml) (99%) compared with the pretreatment HCV RNA level, it is advised to stop treatment because an SVR will rarely occur (*figure 1A*).

Table 7. *Recommendations given by the manufacturer for dosing and duration of combination therapy with peginterferon-alpha-2a and ribavirin*[38,39]

HCV genotype	RVR	HCV RNA at start of therapy	Peginterferon-alpha-2a (weekly)	Weight (kg)	Ribavirin (daily)	Treatment duration (weeks)
Genotype 1	Yes	≤600,000 IU/ml	180 µg	<75 kg ≥75 kg	1000 1200	24 or 48
		>600,000 IU/ml	180 µg	<75 kg ≥75 kg	1000 1200	48
	No	-	180 µg	<75 kg ≥75 kg	1000 1200	48
Genotype 2 or 3	-	-	180 µg		800 mg*	24
Genotype 4	Yes	-	180 µg	<75 kg ≥75 kg	1000 1200	24 or 48
	No	-	180 µg	<75 kg ≥75 kg	1000 1200	48

RVR = rapid viral response (HCV RNA ≤50 IU/ml after 4 weeks). *Retrospective studies with peginterferon-alpha-2b show higher SVR rates with weight-based dosing of ribavirin in patients with genotype 2 or 3.[70,71]

Table 8. *Recommendations given by the manufacturer for dosing and duration of combination therapy with peginterferon-alpha-2a and ribavirin*[46,47]

HCV genotype	RVR	HCV RNA at start of therapy	Peginterferon-alpha-2b (weekly)	Weight (kg)	Ribavirin (mg/day)	Treatment duration (weeks)
Genotype 1	Yes	≤600,000 IU/ml	1.5 µg/kg	<65 65-85 >85	800 1000 1200	24 or 48
		>600,000 IU/ml	1.5 µg/kg	<65 65-85 >85	800 1000 1200	48
	No	-	1.5 µg/kg	<65 65-85 >85	800 1000 1200	48
Genotype 2 or 3		-	1.5 µg/kg	<65 65-85 >85	800 1000 1200	24
Genotype 4	Yes	-	1.5 µg/kg	<65 65-85 >85	800 1000 1200	24 or 48
	No	-	1.5 µg/kg	<65 65-85 >85	800 1000 1200	48

RVR = rapid viral response (HCV RNA ≤50 IU/ml at week 4); EVR = early viral response (HCV RNA 2 $\log_{10}$ IU/ml (copies/ml 99%) decline at week 12).

Shortened antiviral treatment of HCV genotype 1

In patients with HCV RNA load less than 600,000 IU/ml at the start of treatment, who have an undetectable HCV RNA load with a qualitative PCR test at week 4 (rapid viral response, RVR), a shorter treatment of 24 weeks is as effective as a treatment of 48 weeks (*figure 1A*).[64,72,73]

Antiviral therapy of HCV genotype 2 and 3

The treatment of HCV genotype 2 and 3 consists of the administration of peginterferon-α-2a 180 µg/week in combination with 800 mg ribavirin daily or peginterferon-α-2b at a weekly dose of 1.5 µg/kg in combination with weight-based ribavirin (*tables 7* and *8*). The duration of antiviral therapy is 24 weeks.

Shortened antiviral treatment of HCV genotype 2 and 3

Three randomised trials and one nonrandomised trial have shown that patients with genotype 2 and 3 with undetectable HCV RNA, by qualitative PCR after four weeks (RVR), can stop antiviral treatment after 12 to 16 weeks (*figure 1C*).[74-83] Of all patients with genotype 2 and 3, 63 to 78% achieve an RVR and can receive a shorter treatment of 12 to 16 weeks, resulting in SVR rates of 71 to 100%.[74-83] One study testing shorter treatment found a slightly higher relapse rate (statistically not significant).[77] However, for most patients with an RVR, 12 weeks of treatment turned out to be sufficient and nine out of ten patients with a relapse achieved an SVR after retreatment for 24 weeks.[77] The two other randomised trials showed no difference between the relapse rate after 16 or 24 weeks of treatment.[74,82] In all published trials investigating 12 to 16 weeks of treatment, weight-based ribavirin dosing (1000 to 1200 mg/day) was used.[74-83]

Shorter treatment in patients with genotype 2 and 3 with an RVR is not yet registered, but is recommended internationally.[9,22,84] In practice, this means that a shorter treatment can be considered in patients with an RVR who suffer from significant side effects.

Antiviral therapy of HCV genotype 4

The treatment of HCV genotype 4 consists of the administration of peginterferon-α-2a 180 µg/week in combination with weight-based ribavirin daily (1000 mg for <75 kg, 1200 mg for ≥75 kg) or peginterferon-α-2b at a weekly dose of 1.5 µg/kg in combination with weight-based ribavirin (*tables 7* and *8*). The duration of antiviral therapy is 48 weeks. After 12 weeks of antiviral therapy HCV RNA should be tested to determine the viral response. If the HCV RNA level at week 12 has decreased by less than 2 $\log_{10}$ IU/ml (c/ml) (99%) compared with the pretreatment HCV RNA level, it is advised to stop treatment because an SVR will rarely occur (*figure 1B*). After 24 weeks of antiviral therapy HCV RNA should be tested again: if HCV RNA is detectable it is advised to stop treatment because achieving an SVR is rare (*figure 1B*).

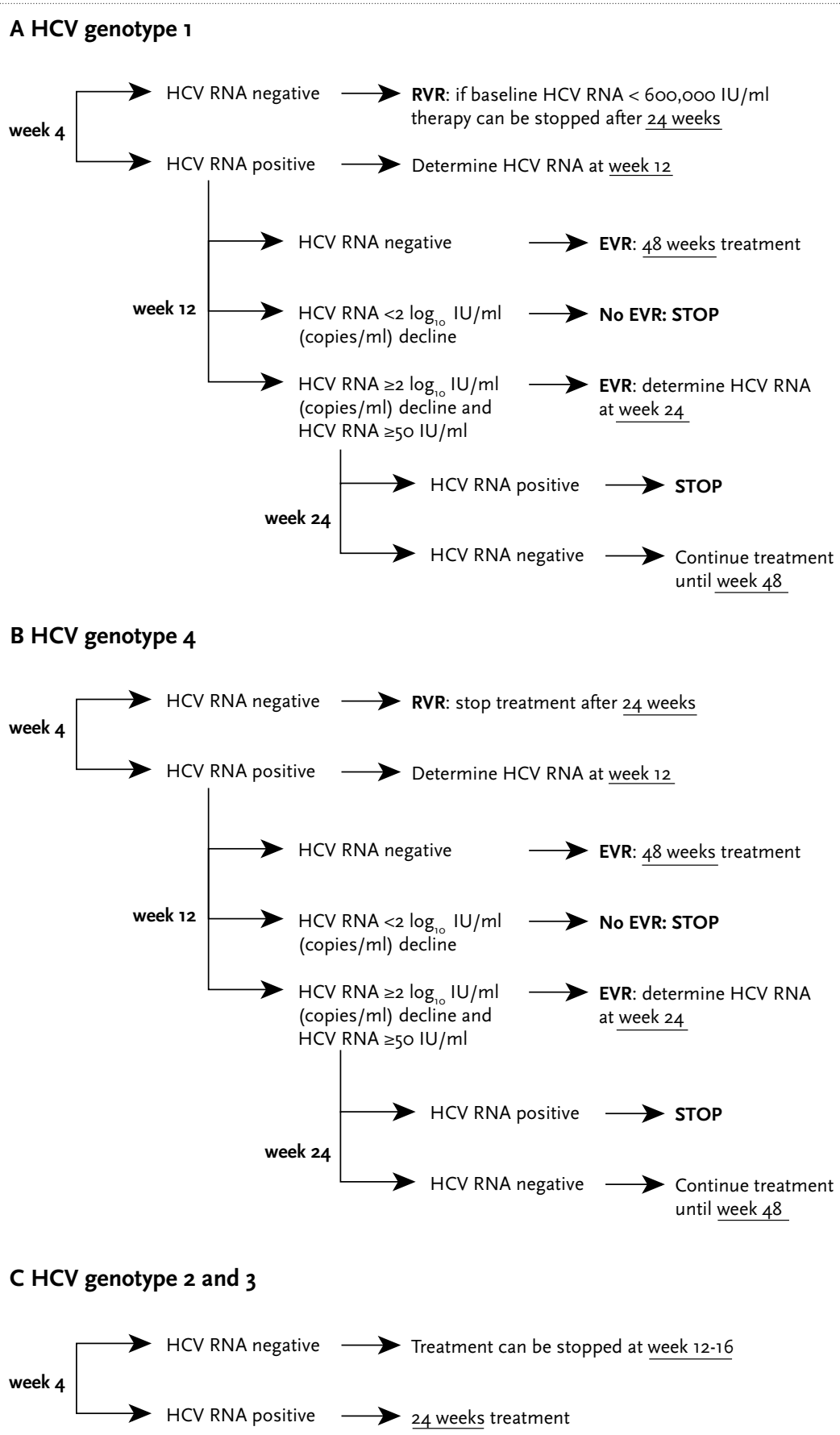
Shortened antiviral treatment of HCV genotype 4

In patients who have undetectable HCV RNA by qualitative PCR test at week 4 (RVR), a shorter treatment of 24 weeks is as effective as treatment for 48 weeks (*figure 1B*).[60,73]

Antiviral therapy of HCV genotype 5 and 6

Limited data are available concerning the optimal treatment of HCV genotype 5 and 6. It is recommended to treat HCV genotype 5 and 6 like HCV genotype 1 (48 weeks).

Figure 1. *Flowchart for the treatment of chronic hepatitis C*[22]



Recommendations	
Antiviral therapy consists of the administration of peginterferon and ribavirin for 24 or 48 weeks. Patients with HCV genotype 1 or 4 are treated for 48 weeks. Patients with HCV genotype 2 or 3 are treated for 24 weeks.	Level 1
In patients with an undetectable HCV RNA after 4 weeks of treatment and baseline HCV RNA <600,000 IU/ml, a shorter treatment is equally effective (12 to 16 weeks for HCV genotype 2 or 3, 24 weeks for HCV genotype 1 or 4 with baseline HCV RNA ≤600,000 IU/ml).	Level 1

FOLLOW-UP DURING ANTIVIRAL THERAPY

Patients who are treated with peginterferon and ribavirin should be monitored regularly at an outpatient clinic to evaluate the viral response and to monitor side effects (at the start, after 2, 4, 8 and 12 weeks of treatment, and afterwards every four to six weeks until the end of treatment; *table 3*). Blood tests (liver enzymes, glucose and full blood cell count) should be routinely done at every visit. Physical examination should be performed when indicated; it is recommended to assess the patient's weight at every visit. Every 12 weeks TSH should be assessed (*table 3*).[85] To keep the treatment as short as possible, HCV RNA should be tested at fixed time points (*table 5*). The HCV RNA load should be determined at the start and after 4, 12, 24 and 48 weeks of treatment (if treatment duration is 48 weeks; *tables 3* and *5*). Antiviral therapy can be stopped earlier if patients have no chance of achieving an SVR.[8,66,86] and in patients who develop an RVR which warrants shorter treatment (*table 5*).[60,62,73] The time it takes for patients to become HCV RNA negative is the strongest predictor for successful outcome of antiviral therapy, independent of the genotype.[62,64,72-74,77,82,83,86,87] For reliable application of stopping rules at the various time points during treatment, it is necessary that baseline HCV RNA load is determined shortly before treatment. In patients with cirrhosis, abdominal ultrasound of the liver should be done every six months during treatment.

Recommendations	
Monitoring is recommended at the start of treatment with peginterferon and ribavirin, after 2, 4, 8 and 12 weeks of treatment, and thereafter every 4 to 6 weeks until the end of treatment.	Level 2
HCV RNA assessment is recommended at the start of treatment, after 4, 12, 24 and 48 weeks of treatment, and 24 weeks after completion of treatment.	Level 1
Based on HCV RNA load at the start and after 4 weeks (28 days) of treatment, shortened treatment can be considered. HCV RNA assessment after 12 and 24 weeks should serve to predict non-SVR and antiviral therapy should be stopped early according to the stopping rules.	Level 1

Side effects

The most important side effects during treatment with peginterferon and ribavirin are flu-like symptoms, depression, anaemia and neutropenia. Dose reduction is indicated in case of serious anaemia, thrombocytopenia or neutropenia (see paragraph about dose reduction and *table 9*). An overview of the most important side effects can be found in *table 6*. Intensive supportive care during treatment contributes to therapy compliance of patients and reduces the chance of premature discontinuation of treatment. Supportive care can be given by the treating physician and/or a specialised nurse. Supportive care of patients should preferably be provided by dedicated nurses, who should be easily accessible for the patient. Patients with significant side effects should be monitored more often at the outpatient clinic. If side effects occur, it is important to have easy access to other specialists (psychiatrist, dermatologist, ophthalmologist, dietician, social work).

Dose reduction of peginterferon and/or ribavirin

Leucopoenia, anaemia and thrombocytopenia are frequent side effects of combination therapy with peginterferon and ribavirin. Dose reduction of peginterferon and ribavirin reduces the chance of an SVR.[88] Dose reduction should therefore only be applied when strictly indicated (*table 9*),[89] anaemia can be treated initially with erythropoietin and subsequently with blood transfusion. Although

Table 9. *Recommendations for dose reduction during antiviral therapy*

	Peginterferon-alpha-2a/2b	Ribavirin	Other treatments
Anaemia			
• Hb <5.0 mmol/l	-	-	Erythropoietin
• Hb <4.0 mmol/l	-	Dose to 800 mg/day	Transfusion and erythropoietin
Neutropenia			
• Neutrophil granulocytes <0.75 x 10^9/l	Dose to 75%	-	-
• Neutrophil granulocytes <0.375 x 10^9/l	Dose to 50%	-	-
Thrombocytopenia			
• Thrombocytes <50 x 10^9/l	Dose to 75%	-	-
• Thrombocytes <25 x 10^9/l	Dose to 50%	-	-

Modified to Bezemer *et al.*,[89] evidence value grade 4.

severe consequences of thrombocytopenia (bleeding) and neutropenia (infection) during treatment with peginterferon and ribavirin have not been observed,[90-92] it is recommended to reduce the dose and to monitor the patient more frequently if thrombocytopenia or neutropenia occurs. The peginterferon and ribavirin dose should be increased again if blood cell count has normalised.

FOLLOW-UP AFTER ANTIVIRAL THERAPY

HCV RNA should be determined with a qualitative PCR test (sensitivity of ≤50 IU/ml) 24 weeks after stopping antiviral therapy; a negative result indicates an SVR. Routine blood tests (liver enzymes, full blood cell count, TSH) should also be determined. Physical examination should be done when indicated. Monitoring should be continued in cirrhotic patients with an SVR because of the risk (reduced but still present) of HCC and decompensated cirrhosis. Noncirrhotic patients with an SVR can be discharged from the outpatient clinic. In these patients, HCV RNA testing can be considered after one to two years, since the chance of a late relapse is around 1 to 5%.[63] Monitoring should be continued in patients with nonresponse, breakthrough or relapse.

Hypothyroidism can occur after stopping antiviral therapy with peginterferon and ribavirin, therefore the TSH level should be determined in all patients one or two years after treatment.[93] Hypothyroidism during treatment with peginterferon and ribavirin is often reversible. Patients who developed hypothyroidism and receive thyroid hormone treatment may stop the hormone suppletion one or two years after antiviral treatment.[94-97]

THE FUTURE

Several specific inhibitors of viral enzymes (the NS3 serineprotease, NS3 helicase, NS5B RNA-polymerase), therapeutic vaccination, Toll-like-receptor agonists and other immune modulators, monoclonal and polyclonal antibodies, antisense RNA, modified forms of interferon and ribavirin and other molecules are currently being tested in phase I, II, III and IV clinical trials.[98-103]

Some of these drugs are promising. These new specific-HCV inhibitors are referred to as STAT-C (specifically targeted antiviral therapy for HCV). It is expected that the first new-generation anti-HCV drugs will be registered within the next three years. Treatment of chronic hepatitis C infection will probably be more effective and shorter. New treatment regimes will probably consist of a combination of peginterferon and ribavirin together with one or more new drugs.

HCV genotype 1 is the most difficult to treat and the most prevalent genotype in Europe, North America and Japan. Therefore, some of the new drugs are specially developed for HCV genotype 1. This means that antiviral therapy may be postponed in patients with HCV genotype 1 infection without a strict indication for antiviral therapy; or these patients can participate in clinical trials where new drugs are being investigated.

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NOTE

Guidelines Committee for the Netherlands Association of Gastroenterologists and Hepatologists: H.L.A. Janssen, chairman; E.H.C.J. Buster, H.C. Gelderblom, secretaries; C.M. Bakker, J.T. Brouwer, K.J. van Erpecum, R.J. de Knegt, H.W. Reesink, S.W. Schalm, H.L. Zaaijer, members.

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