EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines: Management of hepatitis C virus infection

European Association for the Study of the Liver [1]

1. Introduction

Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease worldwide [1]. The long-term hepatic impact of HCV infection is highly variable, from minimal changes to chronic hepatitis, extensive fibrosis, and cirrhosis with or without hepatocellular carcinoma (HCC). The number of chronically infected persons worldwide may exceed 200 million, but most of them have no knowledge of their infection or of the ensuing hepatic condition. Clinical care for patients with HCV-related liver disease has advanced considerably during the last two decades, as a result of growing knowledge about the mechanisms of the disease, remarkable developments in diagnostic procedures, and advances in therapeutic and preventative approaches. Still, various aspects are not yet completely resolved.

These EASL Clinical Practice Guidelines (CPGs) are intended to assist physicians and other healthcare providers, as well as patients and interested individuals, in the clinical decision-making process by describing optimal management of patients with acute and chronic HCV infections. These guidelines apply to therapies that are approved at the time of their publication. Several new therapeutic options have completed phase III development for patients infected with HCV genotype 1 and are currently awaiting licensing and approval in Europe and the United States. Therefore, the EASL CPGs on the management of HCV infection will be updated on a regular basis upon approval of additional novel therapies.

2. Context

2.1. Epidemiology and public health burden

It is estimated that approximately 130–210 million individuals, i.e. 3% of the world population, are chronically infected with HCV [1,2]. The prevalence varies markedly from one geographic area to another and within the population assessed. In Western Europe, HCV prevalence ranges from 0.4% to 3%. It is higher in Eastern Europe and the Middle East, where the numbers are not precisely known [3]. Egypt has the highest worldwide prevalence, with 9% countrywide and up to 50% in certain rural areas, due to specific modes of infection [4]. Prior to the 1990's, the principal routes of HCV infection were via blood transfusion, unsafe injection procedures, and intravenous drug use. These modes of acquisition are estimated to account for approximately 70% of cases in industrialized countries. Screening of blood products for HCV by means of enzyme immunoassays and, in a number of European countries, nucleic acid testing, has virtually eradicated transfusion-transmitted hepatitis C. Currently, new HCV infections are primarily due to intravenous or nasal drug use, and to a lesser degree to unsafe medical or surgical procedures. Parenteral transmission via tattooing or acupuncture with unsafe materials is also implicated in occasional transmissions. The risk of perinatal and of heterosexual transmission is low, while recent data indicate that promiscuous male homosexual activity is related to HCV infection [5].

Six HCV genotypes, numbered 1–6, and a large number of subtypes have been described [6]. They originated from diverse areas in Africa and Asia, and some of them have spread widely throughout the world. Genotype 1 (subtypes 1a and 1b) is by far the most prevalent genotype worldwide, with a higher prevalence of 1b in Europe and 1a in the US. Genotype 3a is highly prevalent in European intravenous drug users [3]. This group is currently experiencing an increasing incidence and prevalence of infections related to HCV genotype 4. Genotype 2 is found in clusters in the Mediterranean region, while 5 and 6 are more rarely found [7].

2.2. Natural history

Acute HCV infection is asymptomatic in 50–90% of cases. Failure to spontaneously eradicate infection occurs in 50–90% of cases according to the route of transmission, the presence of symptomatic hepatitis, and to the age at which infection occurred [8,9]. In Europe, HCV infection is responsible for about 10% of cases of acute hepatitis [3]. The incidence of acute HCV infection has decreased and is now about 1/100,000 subjects per year, but this figure is probably underestimated because it may exclude asymptomatic infections. Chronic infection is associated with variable degrees of hepatic inflammation and fibrosis progression, regardless of

Received 24 February 2011; accepted 24 February 2011

[1] Correspondence: EASL Office, 7 rue des Battoirs, CH 1205 Geneva, Switzerland. Tel.: +41 22 807 0360; fax: +41 22 328 0724.
E-mail address: easloffice@easloffice.eu

Abbreviations: SoC, standard of care; TE, transient elastography; HCV, hepatitis C virus; HBV, hepatitis B virus; HIV, human immunodeficiency virus; PCR, polymerase chain reaction; EIA, enzyme immuno assay; INR, international normalized ratio.

Clinical Practice Guidelines Panel:
Contributors: Antonio Craxì (Coordinator), Jean-Michel Pawlotsky (EASL Governing Board), Heiner Wedemeyer (EASL Governing Board); Kristian Bjoro, Robert Flisiak, Xavier Forns, Mario Mondelli (Journal of Hepatology), Marcus Peck-Radosavljevic, William Rosenberg, Christoph Sarrazin. *Reviewers*: The EASL Governing Board, Ira Jacobson, Geoffrey Dusheiko.

HCV genotype and of viral load. Only exceptionally does it resolve spontaneously. Liver disease progression takes place over several decades, and is accelerated in the presence of cofactors such as alcohol consumption, diabetes mellitus (to which HCV itself appears to predispose), older age of acquisition, human immunodeficiency virus (HIV) coinfection, or coinfection with other hepatotropic viruses. Depending on the presence of co-factors, between 10% and 40% of patients with chronic HCV infection will develop cirrhosis [10]. Death related to the complications of cirrhosis may occur, at an incidence of approximately 4% per year, whereas HCC occurs in this population at an estimated incidence of 1–5% per year [11]. Patients diagnosed with HCC have a 33% probability of death during the first year [12,13].

HCV infection has become the leading cause of primary liver cancers in Europe. Based on models from France to predict the death rates due to HCV-related HCC, the peak mortality related to HCV infection is ahead of us [14] and currently available therapies are expected to have a modest impact on the mortality rate [15]. These results probably also apply to most other European countries.

Extrahepatic manifestations including cryoglobulinaemia, lichen planus, porphyria cutanea tarda, lymphocytic sialoadenitis, and membranous glomerulonephritis may occur. There is an association between non-Hodgkin lymphoma and hepatitis C infection [16].

2.3. Available tools for diagnosis, assessment of disease severity, and monitoring

2.3.1. Virological tools

Diagnosis of chronic HCV infection is based on the presence of both anti-HCV antibodies, detected by enzyme immunoassays, and HCV RNA, detected by molecular assays. HCV RNA testing is essential for the management of HCV therapy [17]. The most recent assays are based on the use of real-time polymerase chain reaction (PCR). They can detect minute amounts of HCV RNA (down to 10 international units (IU)/ml) and accurately quantify HCV RNA levels up to approximately 10^7 IU/ml. Their dynamic range of quantification adequately covers the clinical needs for diagnosis and monitoring [18–20]. When new drugs such as direct acting antivirals become available, high sensitivity levels will become of major importance for characterization of virological responses and treatment decisions and it will be necessary to redefine how low-range HCV RNA results are reported.

HCV genotype and subtype can be determined via various methods, including direct sequence analysis, reverse hybridization, and genotype-specific real-time PCR [17]. The available commercial assays have been shown to accurately identify the six HCV genotypes. However, assays targeting the 5′ noncoding region of the HCV genome fail to differentiate HCV subtypes 1a and 1b in a substantial proportion of patients. Correct subtype identification, the importance of which may increase once new direct acting antivirals will be available, therefore, requires sequence or reverse hybridization-based methods targeting segments other than the 5′ noncoding region [21].

2.3.2. Assessment of liver disease severity

Assessment of the severity of hepatic fibrosis is important in decision making in chronic hepatitis C treatment and prognosis. Liver biopsy is still regarded as the reference method to assess the grade of inflammation and the stage of fibrosis [22,23]. The shortcomings of biopsy have been highlighted in recent years and alternate non-invasive methods have been developed and extensively evaluated in patients with chronic HCV infection. They include serological markers and transient elastography [24,25]. Their performance, when used alone or together, has been reported to be comparable with liver biopsy [24,25]. Both non-invasive methods have been shown to accurately identify patients with mild fibrosis or cirrhosis. They are less able to discriminate moderate and severe fibrosis.

2.3.3. Host genetics

Several independent genome-wide association studies have demonstrated that host polymorphisms located upstream of the IL28B (interferon lambda 3) gene are associated with sustained virological response to treatment with pegylated interferon alpha in combination with ribavirin [26–29]. These polymorphisms are also associated with spontaneous clearance of acute HCV infection, in particular in asymptomatic patients [30,31]. The distribution of IL28B polymorphisms varies between different populations worldwide and helps to explain heterogeneity in response to interferon-based treatments in different ethnic or racial groups [30]. Determination of IL28B polymorphisms may be useful to identify a patient's likelihood of response to treatment with pegylated interferon alpha and ribavirin; however, the predictive value is low. Other genetic variants may also bear some correlation with disease progression in response to treatment.

2.4. The current standard of care and developing therapies.

The primary goal of HCV therapy is to cure the infection, which results in eliminating detectable circulating HCV after cessation of treatment. Sustained virological response (SVR), is defined as an undetectable HCV RNA level (<50 IU/ml) 24 weeks after treatment withdrawal. SVR is generally associated with resolution of liver disease in patients without cirrhosis. Patients with cirrhosis remain at risk of life-threatening complications; particularly, HCC may occur even after viral infection has been eradicated. The combination of pegylated interferon (IFN)-α and ribavirin is the approved and well accepted standard-of-care (SoC) for chronic hepatitis C [32–36]. In patients infected with HCV genotype 1, SVR rates after SoC are on the order of 40% in North America and 50% in Western Europe in most trials. The SVR rates are considerably higher in patients infected with HCV genotypes 2, 3, 5, and 6 (on the order of 80% and are higher for genotype 2 than genotypes 3, 5, and 6). The results of therapy for genotype 4 infected patients approximate those for genotype 1 or are slightly better in HCV genotype 4 infected patients [7].

Two pegylated IFN-α molecules can be used in combination with ribavirin, i.e. pegylated IFN-α2a and pegylated IFN-α2b. The pharmacokinetics of these compounds differs. A large-scale post-approval US trial comparing various schedules of administration of pegylated IFN-α2a and IFN-α2b with ribavirin in patients infected with HCV genotype 1 showed no significant difference between the tested strategies [37]. In contrast, two Italian trials in patients infected with HCV genotypes 1, 2, 3, and 4 showed some benefit, mostly in genotype 1 patients, in favor of pegylated IFN-α2a in combination with ribavirin [38,39]. Although efficacy is still debated, there is currently no conclusive evidence that one pegylated IFN-α should be preferred to the other one as first-line therapy.

A large number of drugs for HCV are at various stages of preclinical and clinical development [40]. New therapeutic strategies aim toward higher efficacy, shortened treatment, easier administration, and improved tolerability and patient adherence. Phase III studies have recently been reported for two NS3/4 protease inhibitors, telaprevir and boceprevir, in combination with pegylated IFN-α and ribavirin in both naïve and non-responder patients infected with HCV genotype 1 [41–44]. These triple therapies are likely to be approved by the EMA and the FDA in late 2011, and to radically change treatment strategies for patients with chronic hepatitis due to HCV genotype 1 in countries that will have access to them (see Section 4.18). Other direct acting antiviral drugs are at earlier stages of clinical development, including additional protease inhibitors, nucleoside/nucleotide analogues and non-nucleoside inhibitors of the HCV RNA-dependent RNA polymerase, NS5A inhibitors, and cyclophilin inhibitors. IFN-sparing regimens, with or without ribavirin, are also currently being tested.

3. Methodology

These EASL CPGs have been developed by a CPG Panel of experts chosen by the EASL Governing Board; the recommendations were peer-reviewed by external expert reviewers and approved by the EASL Governing Board. The CPGs were established using data collected from PubMed and Cochrane database searches before December 2010. The CPGs have been based as far as possible on evidence from existing publications, and, if evidence was unavailable, the experts personal experience and opinion. Where possible, the level of evidence and recommendation are cited. The evidence and recommendations in these guidelines have been graded according to the Grading of Recommendations Assessment Development and Evaluation (GRADE) system. The strength of recommendations thus reflects the quality of underlying evidence. The principles of the GRADE system have been enunciated. The quality of the evidence in the CPG has been classified in one of three levels: high (A), moderate (B) or low (C). The GRADE system offers two grades of recommendation: strong (1) or weak (2) (Table 1). The CPGs thus consider the quality of evidence: the higher the quality of evidence, the more likely a strong recommendation is warranted; the greater the variability in values and preferences, or the greater the uncertainty, the more likely a weaker recommendation is warranted.

The HCV CPG Panel has considered the following questions:

- How should acute and chronic hepatitis C be diagnosed?
- What are the goals and endpoints of treatment?
- What are the results of current therapies and the predictors of response?
- How should patients be assessed before therapy?
- What are the contra-indications to therapy?
- Who should be treated?
- What first-line treatment should be prescribed?
- How should treatment be managed?
- How should treatment be tailored to the virological response?
- How can success rates of SoC be improved?
- How should patients with SVR be followed?
- What should be offered to non-sustained responders to SoC?
- How should patients with severe liver disease be treated?
- How should special groups of patients be treated?
- How should we treat patients with acute hepatitis C?
- How should untreated patients and non-sustained responders be followed?
- What are the perspectives of new treatments?

4. Guidelines

4.1. Diagnosis of acute and chronic hepatitis C

Diagnosis of HCV infection is based on detection of anti-HCV antibodies by enzyme immunoassay and detection of HCV RNA by a sensitive molecular method (lower limit of detection <50 IU/ml), ideally a real-time PCR assay.

The diagnosis of chronic hepatitis C is based on the detection of HCV infection (positive anti-HCV antibodies and HCV RNA) in a patient with signs of chronic hepatitis. Rarely, in profoundly immunosuppressed patients, anti-HCV antibodies are not detected and HCV RNA is present alone.

Recommendations

(1) A detailed history and physical examination is essential (A2) and patients should be queried about alcohol consumption (A1).

Table 1. Evidence grading used in the EASL HCV Clinical Practice Guidelines (adapted from the GRADE system).

Evidence	Notes	
High quality	Further research is very unlikely to change our confidence in the estimate of effect	A
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate	B
Low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any change of estimate is uncertain	C
Recommendation	**Notes**	
Strong	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost	1
Weak	Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption	2

(2) Diagnosis of HCV infection is based on detection of anti-HCV antibodies by EIA and HCV RNA by a sensitive molecular method (A1).
(3) For the diagnosis of acute hepatitis C, HCV RNA testing is required since HCV RNA appears before anti-HCV antibodies may be detectable (A2).
(4) Anti-HCV positive, HCV RNA negative patients with acute hepatitis should be retested a few weeks later (B2).
(5) Anti-HCV and HCV RNA positivity does not differentiate acute hepatitis C from exacerbation of chronic hepatitis C or from acute hepatitis from other causes in a patient with chronic hepatitis C (B2).
(6) Chronic hepatitis C should be proven by the presence of both anti-HCV antibodies and HCV RNA (A1).
(7) Immunosuppressed patients may require a test for HCV RNA if hepatitis is present but anti-HCV antibodies are undetectable (B2).

4.1.1. Prevention of HCV transmission and vaccination against HAV and HBV

There are currently no vaccines available for the prevention of HCV infection [45]. Thus, HCV transmission can only be avoided by education and strict adherence to hygienic standards. The risk for HCV transmission is usually related to the level of HCV viral load. Genetic factors may also contribute to the susceptibility for HCV infection.

Seroconversion to anti-HCV occurs in less than 1% of occupational exposures to HCV [46]. In addition, medical treatment still represents a risk factor for HCV transmission even in Western countries [47,48]. Acute HBV and HAV superinfection may take a more severe course in patients with chronic hepatitis C although conflicting data have been published [49–53]. The risk for sexual transmission of HCV is very low although recent data indicate that promiscuous male homosexual activity is related to HCV infection [5]. The vertical transmission rate of HCV is low (1–6%). Transmission might be higher for girls than for boys and in HIV-positive mothers [54] with high HCV viral load.

Recommendations

(1) Persons who experienced an injury with an HCV-contaminated needle should be tested for HCV RNA within 4 weeks. Anti-HCV and ALT testing should be performed after 12 and 24 weeks (B2).
(2) HCV infected persons should not share potentially blood-contaminated tools such as shavers, scissors, tooth brushes, or needles with any other person (A1).
(3) Medical health professionals should be tested for anti-HCV. HCV RNA-positive health professionals should avoid activities with an increased risk of accidental puncture or break of skin or mucosa (C2).
(4) Family members of HCV-infected patients should be tested at least once for anti-HCV (C1).
(5) The use of condoms during sexual intercourse is recommended only for promiscuous individuals and homosexual men (A1).
(6) Drug users should be educated about modes of HCV transmission. They should be tested regularly for anti-HCV. Sterile needles should be provided (B2).
(7) Caesarean sections are not recommended for HCV-infected pregnant women to prevent vertical HCV transmission. Children of HCV-infected mothers should be tested for HCV-RNA 1 month after birth as passively transmitted maternal anti-HCV antibodies can persist in their blood for several months after birth. Mothers with chronic hepatitis C are allowed to breast-feed their children as long as they are negative for HIV and do not use intravenous drugs (B2).
(8) Patients with chronic hepatitis C should be vaccinated against HAV and HBV (B2).

4.2. Goals and endpoints of HCV therapy

The goal of therapy is to eradicate HCV infection in order to prevent the complications of HCV-related liver disease, including necroinflammation, fibrosis, cirrhosis, HCC, and death.

The endpoint of therapy is SVR, intermediate endpoints are used during SoC treatment to assess the likelihood of an SVR and tailor treatment duration. They include HCV RNA level measurements at 4, 12, and 24 weeks of therapy, which are interpreted in comparison to the baseline HCV RNA level. When HCV is eradicated, necroinflammation ceases and fibrosis progression is halted in non-cirrhotic patients.

Recommendations

(1) The goal of therapy is to eradicate HCV infection (A1).
(2) The endpoint of therapy is sustained virological response (A1). Once obtained, SVR usually equates to cure of infection in more than 99% of patients (A1).
(3) Intermediate endpoints to assess the likelihood of an SVR are HCV RNA levels at 4, 12, and 24 weeks of therapy (B2).

4.3. Results of current therapies and predictors of response

4.3.1. Treatment-naïve patients

In the pivotal clinical trials for registration of pegylated IFN-α and ribavirin therapy, SVR was achieved in 46% and 42% of patients infected with HCV genotype 1 treated with pegylated IFN-α2a or pegylated IFN-α2b and ribavirin, respectively [55–57]. SVR rates in these patients were slightly higher in Europe than in the US. These results were confirmed in the IDEAL trial that compared two approved treatment regimens in the United States: 41% with pegylated IFN-α2a, 180 μg/week plus weight-based ribavirin, 1.0–1.2 g/day, vs. 40% with pegylated IFN-α2b, 1.5 μg/kg/week plus weight-based ribavirin, 0.8–1.4 g/day for 48 weeks (NS) [37]. In patients infected with HCV genotypes 2 and 3, SVR was achieved in the pivotal trials in 76% and 82% of cases with pegylated IFN-α2a plus ribavirin and pegylated IFN-α2b plus ribavirin, respectively. A recent meta-analysis showed higher SVR rates in genotype 2 than in genotype 3 infected patients treated for 24 weeks (74% vs. 69%, respectively) [58]. Some "real-life" studies have recently reported somewhat lower SVR rates, in particular for genotype 3 infection [59].

The strongest predictors of SVR are the recently identified genetic polymorphisms located in chromosome 19, close to the region coding for IL28B (or IFN λ3), the HCV genotype, and the stage of fibrosis. Other predictors of response include baseline HCV RNA levels, the dose and duration of therapy, host factors, such as body mass index, age, insulin resistance, gender, and the characteristics

of liver disease, including levels of ALT, GGT, the stage of fibrosis or co-infection with another hepatotropic virus or with HIV [57].

Summary of evidence

(1) SVR is achieved in 40–54% of patients infected with HCV genotype 1 treated with pegylated IFN-α plus ribavirin at approved doses for 48 weeks (A1).
(2) SVR is achieved in 65–82% of patients infected with HCV genotypes 2 or 3 treated with pegylated IFN-α plus ribavirin at approved doses for 24 weeks (A1).
(3) SVR rates are slightly higher in patients infected with HCV genotype 2 than in those with genotype 3 (B2).
(4) Strongest baseline predictors of SVR are:
   a. HCV genotype (A1).
   b. Genetic polymorphisms located in chromosome 19 (IL28B), particularly in genotype 1 patients (A1).
   c. Stage of liver fibrosis (A1).

4.3.2. Relapsers

Relapsers are defined as patients who achieved an end-of-treatment response (undetectable HCV RNA at the end of treatment) but subsequently relapsed and did not achieve an SVR. The relapse rate after treatment with pegylated IFN-α and ribavirin is on the order of 15–25%, but varies according to when HCV RNA becomes undetectable during therapy.

Patients relapsing after treatment with standard IFN-based regimens respond to re-treatment with pegylated IFN-α and ribavirin in 32–53% of cases [60].

4.3.3. Non-responders

Non-responders are patients who failed to achieve a decline of 2 log HCV RNA IU/ml after 12 weeks of treatment or who never achieved undetectable HCV RNA during treatment of a minimum duration of 24 weeks. In the most recent trials, re-treatment of patients infected with HCV genotype 1 who failed previous pegylated IFN-α and ribavirin therapy ranged from 4% to 14% [61,62].

4.4. Pre-therapeutic assessment

The causal relationship between HCV infection and liver disease must be established, liver disease severity must be assessed, and baseline virological and host parameters that will be useful to tailor therapy should be determined.

4.4.1. Assessment of liver disease

The assessment of liver disease should include biochemical markers, such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase, bilirubin, prothrombin time or INR; albumin; gammaglobulins; full blood counts. Abdominal ultrasound must also be performed.

4.4.2. HCV RNA detection and quantification

HCV RNA must be detectable to confirm the causal role of HCV. When planning treatment, HCV RNA must be quantified at baseline to be subsequently used as a reference in order to tailor treatment duration according to the HCV RNA kinetics. The use of real-time PCR quantification assays is strongly recommended for HCV RNA detection and quantification because of their sensitivity, specificity, accuracy, and broad dynamic range. The World Health Organization (WHO) has defined an international standard for normalization of expression of HCV RNA concentrations. Serum HCV RNA levels should be expressed in IU/ml to ensure comparability. Standardized commercial assays are preferred to non-standardized "in house" technologies, and the same assay should be used in each patient to ensure consistency when evaluating antiviral response.

Recommendation

(1) HCV RNA detection and quantification should be made by a sensitive assay (lower limit of detection of 50 IU/ml or less), ideally a real-time PCR assay, and HCV RNA levels should be expressed in IU/ml (C1).

4.4.3. Search for other causes of liver disease

Other causes of chronic liver diseases should be systematically investigated, including co-infection with HIV and/or other hepatotropic viruses. Co-morbidities, including alcoholic, autoimmune, or metabolic liver disease with steatosis or steatohepatitis should be assessed. It is helpful to exclude pre-existing thyroid disease and thyroid peroxidase antibodies.

Recommendations

(1) The causal relationship between HCV infection and liver disease must be established (B1).

4.4.4. Assessment of liver disease severity

Assessment of liver disease severity is recommended prior to therapy. Identifying patients with cirrhosis is of particular importance, as their likelihood of responding to therapy and post-treatment prognosis are altered, and surveillance for HCC is required. Assessment of the stage of fibrosis by biopsy is not required in patients with clinical evidence of cirrhosis. Since significant fibrosis may be present in patients with repeatedly normal ALT, evaluation of disease severity should be performed regardless of ALT patterns. Endoscopy to rule out esophageal varices and portal hypertension should be performed in patients with known cirrhosis.

Liver biopsy remains the reference method. The risk of severe complications is very low (1/4000–10,000), but biopsy remains an invasive procedure. Histological features (necroinflammation = *grading*; fibrosis = *staging*) should be reported using a structured, semi-quantitative method. Various scoring systems have been validated for use in chronic hepatitis C. The most widely used in Europe are METAVIR, Scheuer, Ishak, and Knodell's HAI [63]. Metavir and Scheuer's scores are more reproducible and less prone to observer variation, but less discriminant both for fibrosis and for necroinflammation than Ishak and Knodell [64].

Based on the abundant literature in chronic hepatitis C, alternative, non-invasive methods can now be used instead of liver biopsy in patients with chronic hepatitis C to assess liver disease severity prior to therapy at a safe level of predictability.

Clinical Practice Guidelines

Transient elastography (TE)[a] can be used to assess liver fibrosis in patients with chronic hepatitis C, provided that consideration is given to factors that may adversely affect its performance such as obesity, age, and biochemical necroinflammatory activity. TE results should be evaluated relative to interquartile range and to the success rate of measurements. TE performs better at detecting cirrhosis than lesser degrees of fibrosis [65,66].

The well established panels of biomarkers of fibrosis can be broadly categorized as those that include commonly performed biochemical and hematological tests, such as ALT, AST, prothrombin time, platelets (APRI, AST/ALT ratio, Forns Index); those that include specific indirect markers of liver fibrosis, such as α-2 macroglobulin[b]; those that incorporate only direct markers of liver fibrosis[c] [70–71], or combinations of direct and indirect markers[d].

Sufficient evidence exists to support the view that simple and combination algorithms perform well in the detection of significant fibrosis (METAVIR score F2-F4). Thus, their use in patients with chronic hepatitis C can be recommended for this purpose. They all perform less well in the detection of lesser degrees of fibrosis [66–69]. The combination of blood tests or the combination of TE and a blood test improve accuracy and reduce the necessity of using liver biopsy to resolve uncertainty. However, they increase the cost [72].

Recommendations

(1) Liver disease severity should be assessed prior to therapy (B1).
(2) Identifying patients with cirrhosis is of particular importance, as their prognosis and likelihood to respond to therapy are altered, and they require surveillance for HCC (A1).
(3) As liver disease can progress in patients with repeatedly normal ALT levels, disease severity evaluation should be performed regardless of ALT levels (B2).
(4) Assessment of the severity of liver fibrosis is important in decision making in patients with chronic hepatitis C (A1).
(5) Liver biopsy is still regarded as the reference method to assess the grade of inflammation and the stage of fibrosis (A2).
(6) Transient elastography (TE) can be used to assess liver fibrosis in patients with chronic hepatitis C (A2).
(7) Non-invasive serum makers can be recommended for the detection of significant fibrosis (METAVIR score F2–F4) (A2).
(8) The combination of blood tests or the combination of transient elastography and a blood test improve accuracy and reduce the necessity of using liver biopsy to resolve uncertainty (C2).

4.4.5. Evaluation of patient's genetic polymorphisms

The HCV genotype should be assessed prior to treatment initiation since it influences decisions on the dose of ribavirin and on duration of treatment. With the current SoC, only the genotype (1–6) should be determined. The reference method is direct sequence analysis of the non-structural 5B region. Overall, last generation commercial genotyping assays based on direct sequence analysis of the 5′ untranslated region or on reverse hybridization of both the 5′ untranslated and core regions are satisfactory to differentiate the HCV genotypes in clinical practice [17]. A need for subtyping may arise in the future due to different genetic barriers in resistance to protease inhibitors of HCV subtypes 1a and 1b [21].

Recommendations

(1) The HCV genotype must be assessed prior to antiviral treatment initiation and will determine the dose of ribavirin and treatment decision (A1).
(2) With SoC, only the genotype (1–6), not the subtype, needs to be determined (A1).

4.4.6. Determination of host genetics

Host polymorphisms located upstream of the IL28B gene are associated with sustained virological response to treatment with pegylated interferon alpha in combination with ribavirin in patients infected with HCV genotype 1 [26–29]. However, the individual predictive value is low. Determination of these polymorphisms may be useful to assess a patient's likelihood of response to treatment with pegylated interferon alpha and ribavirin, but should not be used to defer therapy in those less likely to respond but most in need of treatment, i.e. patients with significant fibrosis. IL28B polymorphisms are less useful in patients with HCV genotype 2 and 3 infections [73,60].

Recommendations

(1) Determination of IL28B polymorphisms may assist in evaluating a patient's likelihood of response to treatment with pegylated interferon alpha and ribavirin (B2).

4.5. Contra-indications to therapy

Treatment of chronic hepatitis C with interferon containing regimens has an absolute contra-indication in patients without an option for liver transplantation in the following groups: uncontrolled depression, psychosis, or epilepsy; uncontrolled autoimmune diseases; (Child–Pugh B7 or more); pregnant women or couples unwilling to comply with adequate contraception; severe concurrent medical disease, such as poorly controlled hypertension, heart failure, poorly controlled diabetes, and chronic obstructive pulmonary disease. Relative contraindications to treatment are abnormal hematological indices (hemoglobin <13 g/dl for men and <12 g/dl for women, neutrophil count <1500/mm^3, platelet count <90,000/mm^3); serum creatinine level >1.5 mg/dl; significant coronary heart disease; and untreated thyroid diseases. Although decompensated patients should usually not be treated, treatment of patients with advanced liver disease (Child B cirrhosis) whose parameters may lie below label recommendations may be feasible in experienced centers under careful monitoring.

Recommendation

(1) Patients with absolute contra-indications to SoC should not receive therapy (A1).

Commercial or brand names for these tests are:
[a] TE: Fibroscan®
[b] Tests including indirect markers of fibrosis: Fibrotest™
[c] Tests including direct markers of fibrosis: Enhanced Liver Fibrosis Test ELF™; MP3™, Fibrospect II™
[d] Tests including combinations of indirect and direct markers of fibrosis: Hepascore™; Fibrometer™

4.6. Indications for treatment: who should be treated?

All treatment-naïve patients with compensated chronic liver disease related to HCV who are willing to be treated and have no contra-indication to pegylated IFN-α or ribavirin should be considered for therapy, whatever their baseline ALT level. Treatment should be initiated in patients with advanced fibrosis (METAVIR score F3–F4), and strongly considered in patients with moderate fibrosis (F2). In the patients with mild liver disease, particularly with longstanding infection, a balance between the benefit and risk related to therapy must be struck, also taking into account the perspective of new drugs and life expectancy of the patient.

Patients infected with HCV genotype 1 who failed to eradicate HCV after prior therapy with pegylated IFN-α and ribavirin should not be re-treated with the same drug regimen, as the SVR rates are low (on the order of 9–15% for all genotypes and 4–6% for genotype 1) [61,62]. These patients should wait for the approval of new combination therapies, which have been shown to yield higher SVR rates, on the order of 30–60%, depending on the type of previous non-response and stage of liver disease [41].

Patients infected with HCV genotypes other than genotype 1 who failed in prior therapy with IFN-α with or without ribavirin can be re-treated with pegylated IFN-α and ribavirin, given the absence of a possibility of new drugs active against non-genotype 1 HCV.

Recommendations

(1) All treatment-naïve patients with compensated disease due to HCV should be considered for therapy (A2).
(2) Treatment should be initiated promptly in patients with advanced fibrosis (METAVIR score F3–F4), and strongly considered in patients with moderate fibrosis (METAVIR score F2) (B2).
(3) In patients with less severe disease, indication for therapy is individual (C2).

4.7. First-line treatment of chronic hepatitis C: What are the treatment recommendations?

The first-line treatment of chronic hepatitis C is based on the use of any of the two pegylated IFN-α available, administered weekly, subcutaneously, and daily oral ribavirin (A1). Pegylated IFN-α2a should be used at a dose of 180 μg once per week, whereas pegylated IFN-α2b should be used at a weight-based dose of 1.5 μg/kg per week. The ribavirin dose depends on the HCV genotype. Patients infected with HCV genotypes 1 and 4–6 should receive a weight-based dose of ribavirin: 15 mg/kg body weight per day. Patients infected with genotypes 2 and 3 can be treated with a flat dose of 800 mg of ribavirin daily, but those with a BMI beyond 25 or who have baseline factors suggesting low responsiveness (insulin resistance, metabolic syndrome, severe fibrosis or cirrhosis, older age) should receive a weight-based dose of ribavirin, similar to genotypes 1 and 4. Strict birth control should be applied in patients treated with pegylated IFN-α and ribavirin during therapy and in the six months following. Treatment with pegylated IFN-α and ribavirin has been deemed cost effective even for early stages of fibrosis [75–77].

Recommendations

(1) The combination of pegylated IFN-α and ribavirin is the approved SoC for chronic hepatitis C (A1).
(2) Two pegylated IFN-α molecules, pegylated IFN-α2a (180 μg once per week) and pegylated IFN-α2b (1.5 μg/kg once per week), can be used in combination with ribavirin.
(3) Ribavirin should be given at a weight-based dose of 15 mg/kg per day for genotypes 1 and 4–6 (A2) and at a flat dose of 800 mg/day for genotypes 2 and 3 (A2).
(4) Patients with genotypes 2 and 3 with baseline factors suggesting low responsiveness should receive weight-based ribavirin at the dose of 15 mg/kg per day (C2).

4.8. Treatment monitoring

Treatment monitoring includes monitoring of treatment efficacy and any side effects.

Recommendations

(1) Patients treated with pegylated IFN-α and ribavirin should be seen at a minimum of weeks 4 and 12 after initiation of treatment then at a minimum of every 12 weeks until the end of treatment for both efficacy and side effects, and 24 weeks after the end of therapy to assess the SVR (C2) [55,78,79].

4.8.1. Monitoring of treatment efficacy

Monitoring of treatment efficacy is based on repeated measurements of HCV RNA levels. A sensitive, accurate assay with a broad dynamic range of quantification, ideally a real-time PCR based assay, should be used. The same assay, ideally from the same laboratory, should be used in each patient to measure HCV RNA at different time points, in order to assure consistency of results [18,74,80].

Abbreviated (24 week treatment) is indicated for patients with genotype 1 and a low vs. high baseline and undetectable HCV RNA after 4 weeks treatment. There is no current agreement on the most discriminatory HCV RNA level, which ranges between 400,000 and 800,000 IU/ml (5.6–5.9 $\log_{10}$ IU/ml) [55,78,81–85].

In order to monitor treatment efficacy and guide decisions on treatment duration, HCV RNA level measurements should be performed at baseline, weeks 4, 12, and 24, at the end of treatment, and 24 weeks after the end of therapy in order to assess the SVR. ALT levels should be measured at the same time points as HCV RNA levels. The biochemical response (ALT normalization) generally follows the virological response by a few weeks.

Recommendations

(1) A real-time PCR-based assay, with a lower limit of detection of 10–20 IU/ml is the best tool for monitoring therapy (B1).
(2) A low vs. high baseline HCV RNA level is useful to guide treatment decisions (B2). The best discriminating HCV RNA level is comprised between 400,000 and 800,000 IU/ml (C2).
(3) During treatment, HCV RNA measurements should be performed at weeks 4, 12, and 24 to help tailor treatment (A2).
(4) The end-of-treatment virological response and the SVR 24 weeks after the end of treatment must be assessed (A1).

4.8.2. Monitoring of treatment safety

Flu-like symptoms are often present after pegylated IFN-α injections. They are easily controlled by paracetamol and tend to attenuate after 4–6 weeks of therapy.

At each visit, the patients should be assessed for clinical side effects, such as severe fatigue, depression, irritability, sleeping disorders, skin reactions, and dyspnea. Hematological and biochemical side effects of pegylated IFN-α and ribavirin include neutropenia, anemia, thrombocytopenia, and ALT flares. These parameters should be assessed at weeks 1, 2, and 4 of therapy and at 4–8 week intervals thereafter. Thyroid stimulating hormone (TSH) and free thyroxine levels should be measured every 12 weeks while on therapy [57]. Unusual or severe side effects include seizures, bacterial infections, autoimmune reactions, interstitial lung disease, a neuroretinitis, bone marrow aplasia or idiopathic thrombocytopenia. Patients should be advised of the risk of teratogenicity with RBV and the need for contraception for 6 months beyond treatment.

Recommendations

(1) Treatment toxicities should be assessed at weeks 2 and 4 of therapy and at 4–8 week intervals thereafter (C2).

4.9. Treatment dose reductions and stopping rules

The pegylated IFN-α dose should be reduced in case of severe side effects, such as clinical symptoms of severe depression, and if the absolute neutrophil count falls below 750/mm^3, or the platelet count falls below 50,000/mm^3. In individual cases, clinicians may choose to maintain or reduce dosing in these situations but cautious monitoring is advised. When using pegylated IFN-α2a, the dose can be reduced from 180 to 135 μg/week and then to 90 μg/week. When using pegylated IFN-α2b, the dose can be reduced from 1.5 to 1.0 μg/kg/week and then to 0.5 μg/kg/week. Pegylated IFN-α should be stopped in case of marked depression, if the neutrophil count falls below 500/mm^3 or the platelet count falls below 25,000/mm^3. If neutrophil or platelet counts go up, treatment can be re-started, but at a reduced pegylated IFN-α dose. If significant anemia occurs (hemoglobin <10 g/dl), the dose of ribavirin should be adjusted downward by 200 mg at a time. Ribavirin administration should be stopped if the hemoglobin level falls below 8.5 g/dl. Alternatively, growth factors can be used to maintain high doses of pegylated IFN-α and/or ribavirin (see below) [55,56,78,86–90].

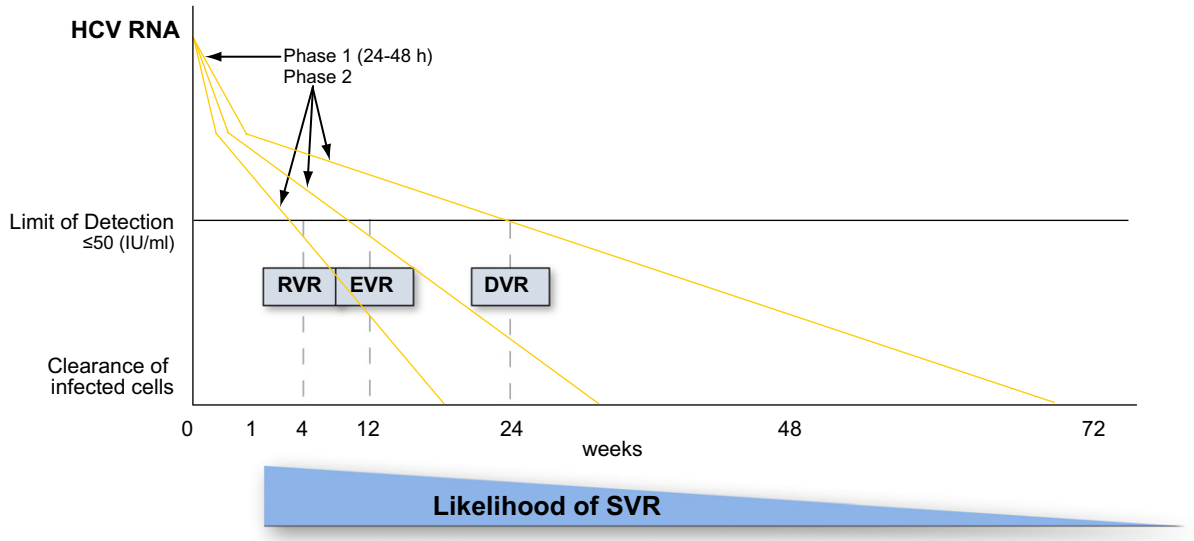
Treatment should be promptly stopped in case of a hepatitis flare (ALT levels above 10 times normal, if not already present at the time of starting treatment) or if a severe bacterial infection occurs at any body site, regardless of neutrophil counts.

Recommendations

(1) The pegylated IFN-α dose should be reduced if the absolute neutrophil count falls below 750/mm^3, or the platelet count falls below 50,000/mm^3, and stopped if the neutrophil count falls below 500/mm^3 or the platelet count falls below 25,000/mm^3 or if severe unmanageable depression develops (C2).
(2) If neutrophil or platelet counts go up, treatment can be re-started, but at a reduced pegylated IFN-α dose (C2).
(3) If hemoglobin <10 g/dl occurs, the dose of ribavirin should be adjusted downward by 200 mg at a time (C2), and ribavirin stopped if hemoglobin falls below 8.5 g/dl.
(4) Treatment should be stopped in case of a severe hepatitis flare or severe sepsis (C2).

4.10. Virological response-guided therapy

Pegylated IFN-α and ribavirin treatment duration can be tailored to the on-treatment virological response. Upon treatment, HCV RNA should be assessed at three time points, regardless of the HCV genotype: baseline, weeks 4 and 12. Week 24 testing may also be useful in selected patients. The likelihood of SVR is directly proportional to the time of HCV RNA disappearance (Fig. 1).



DVR, delayed virological response; EVR, early virological response; RVR, rapid virological response.

Fig. 1. Likelihood of SVR according to viral response in the first weeks of therapy.

Table 2. Monitoring of on-therapy response to PEG IFN plus ribavirin.

Sustained virological response (SVR)	Undectable HCV RNA level (<50 IU/ml), 24 weeks after treatment
Rapid virological response (RVR)	Undectable HCV RNA in a sensitive assay (lower limit of detection ≤50 IU/ml) at week 4 of therapy, maintained up to end of treatment
Early virological response (EVR)	HCV RNA detectable at week 4 but undetectable at week 12, maintained up to end of treatment
Delayed virological response (DVR)	More than 2 $\log_{10}$ drop but detectable HCV RNA at week 12, HCV RNA undetectable at week 24, maintained up to end of treatment
Null response (NR)	Less than 2 $\log_{10}$ IU/ml decrease in HCV RNA level from baseline at 12 weeks of therapy
Partial nonresponse (PR)	More than 2 $\log_{10}$ IU/ml decrease in HCV RNA level from baseline at 12 weeks of therapy but detectable HCV RNA at weeks 12 and 24
Breakthrough (BT)	Reappearance of HCV RNA at any time during treatment after virological response

Treatment should be stopped at week 12 if the HCV RNA decrease is less than 2 $\log_{10}$ IU/ml, i.e. if the baseline HCV RNA level is reduced by less than 99% of the baseline value, as the SVR rate in these patients with standard treatment duration is less than 2%. In patients with detectable HCV RNA ($\geqslant$50 IU/ml) at week 24, treatment should also be stopped due to a minimal chance of SVR (1–3%) [55,78,91,92].

Patients with a more than 2 $\log_{10}$ drop or an undetectable HCV RNA at week 12 can be classified into three groups according to their virological response (Table 2): (1) *rapid virologic response* (RVR) is defined as an undetectable HCV RNA level in a sensitive assay (lower limit of detection $\leqslant$50 IU/ml) at week 4 of therapy (approximately 24–27% of genotype 1 and 64–76% of genotype 2- or 3-infected patients achieve an RVR); (2) *early virological response* (EVR) is defined as an HCV RNA which is detectable at week 4 but undetectable at week 12; (3) *delayed virological response* (DVR) is defined as a more than 2 $\log_{10}$ decline in HCV RNA concentration but a detectable HCV RNA level at week 12 and an undetectable HCV RNA level at week 24 (approximately 22–31% of genotype 1-infected patients have a DVR). Up to the end of any treatment, all types of virological responses (RVR, EVR, DVR) must be followed by assays ensuring that HCV RNA is undetectable. Reappearance of HCV RNA at any time during treatment after virological response is classified as a breakthrough (BT).

The following treatment durations should be applied according to the virological response, regardless of the HCV genotype:

(i) Patients infected with HCV genotype 1 who have an RVR should be treated for 24 weeks if they have a low baseline viral level, as suggested by a recent meta-analysis. As uncertainties remain as to which threshold should be used to distinguish between low and high baseline HCV RNA levels, patients infected with HCV genotype 1 (and possibly also those infected with genotype 4) with a baseline viral level below 400,000–800,000 IU/ml should be treated for 24 weeks, whereas it is reasonable to prolong therapy for a total of 48 weeks in patients with a higher baseline HCV RNA level [56,83–85,93,94].

(ii) Patients infected with HCV genotype 1 (and possibly also those infected with genotype 4) and EVR should be treated for 48 weeks [93,95–100].

(iii) Patients with genotype 1 and a delayed virological response (DVR) can be treated for 72 weeks in the hope of minimizing the risk of relapse, provided that their HCV RNA is undetectable at week 24. Insufficient data exist for other genotypes [93,95–100].

(iv) In patients infected with HCV genotypes 2 and 3 with an RVR and low baseline viral load (<400,000–800,000 IU/ml), shortening of treatment duration to 16 weeks can be considered at the expense of a slightly higher chance of post-treatment relapse [81,101–104].

(v) In patients with HCV genotypes 2 and 3 who have advanced fibrosis, cirrhosis or cofactors affecting response (insulin resistance, metabolic syndrome, non-viral steatosis) shortening of treatment duration to 16 weeks should not be considered even if they have low baseline viral and RVR, due to insufficient evidence for equivalent efficacy [82,105–107].

(vi) Patients with genotypes 2 and 3 and either EVR or DVR or with negative cofactors affecting response could be treated for 48 or 72 weeks, respectively, provided that their HCV RNA is undetectable at week 24 [56].

(vii) No data are available on response guided therapy in patients infected with HCV genotypes 5 and 6. However, these genotypes do generally show similar response rates as compared to HCV genotype 3-infected patients [7,108,109].

Response-guided treatment profiles are outlined in Fig. 2 for genotype 1 and Fig. 3 for genotypes 2 and 3.

Recommendations

(1) Treatment duration should be tailored to the on-treatment virological response at weeks 4 and 12, and eventually week 24. The likelihood of SVR is directly proportional to the time of HCV RNA disappearance (B1).

(2) Treatment for all HCV genotypes should be stopped at week 12 if the HCV RNA decrease is less than 2 $\log_{10}$ IU/ml and at week 24 if HCV RNA is still detectable ($\geqslant$50 IU/ml) (B1).

(3) In patients with a *rapid virologic response* (RVR) and low baseline viral load (<400,000–800,000 IU/ml), treatment for 24 weeks (genotypes 1 and 4) or 12–16 weeks (genotypes 2/3) can be considered. If negative predictors of response (i.e. advanced fibrosis/cirrhosis, metabolic syndrome, insulin resistance, hepatic steatosis) are present, evidence for equal efficacy of shortened treatment is insufficient (B2).

Clinical Practice Guidelines

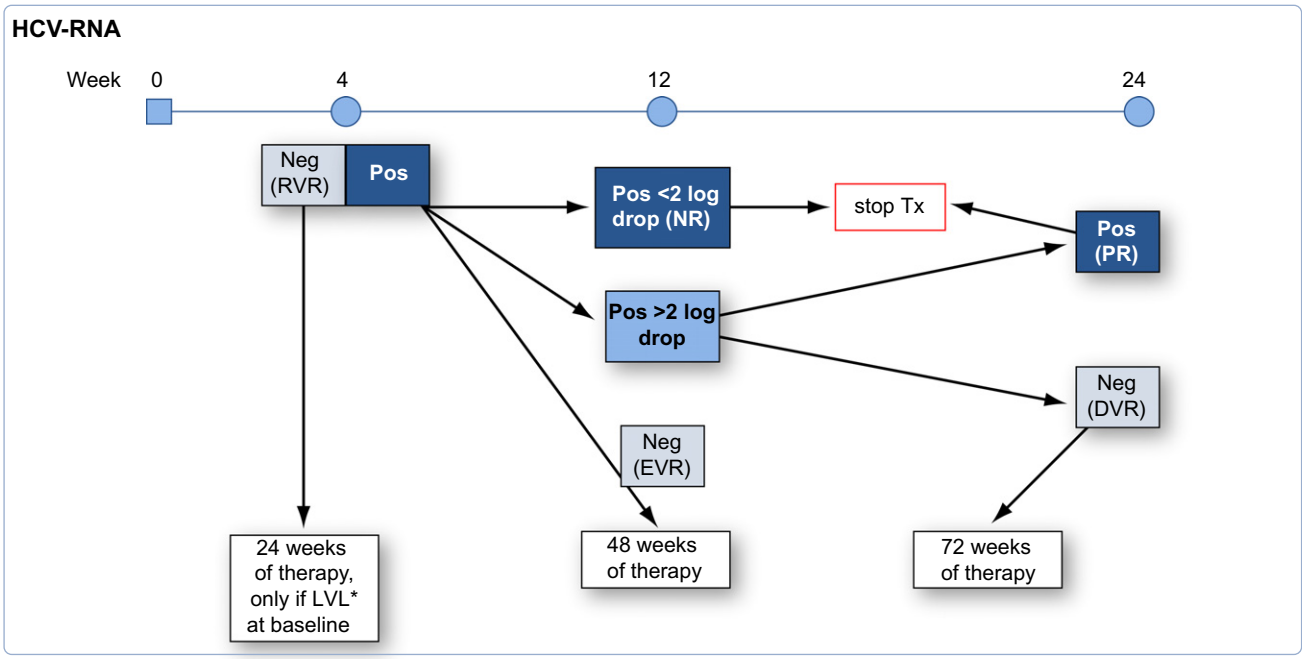


Fig. 2. Response-guided therapy in patients with genotype 1 (applies also to genotype 4 at a B2 grade of evidence).

(4) Patients who have an *early virologic response* (EVR), i.e. HCV RNA which is detectable at week 4 but undetectable at week 12 should be treated for 48 weeks regardless of the HCV genotype and baseline viral load (C2).

(5) Patients with genotype 1 and a *delayed virological response* (DVR) can be treated for 72 weeks (B2). This may also apply to other genotypes.

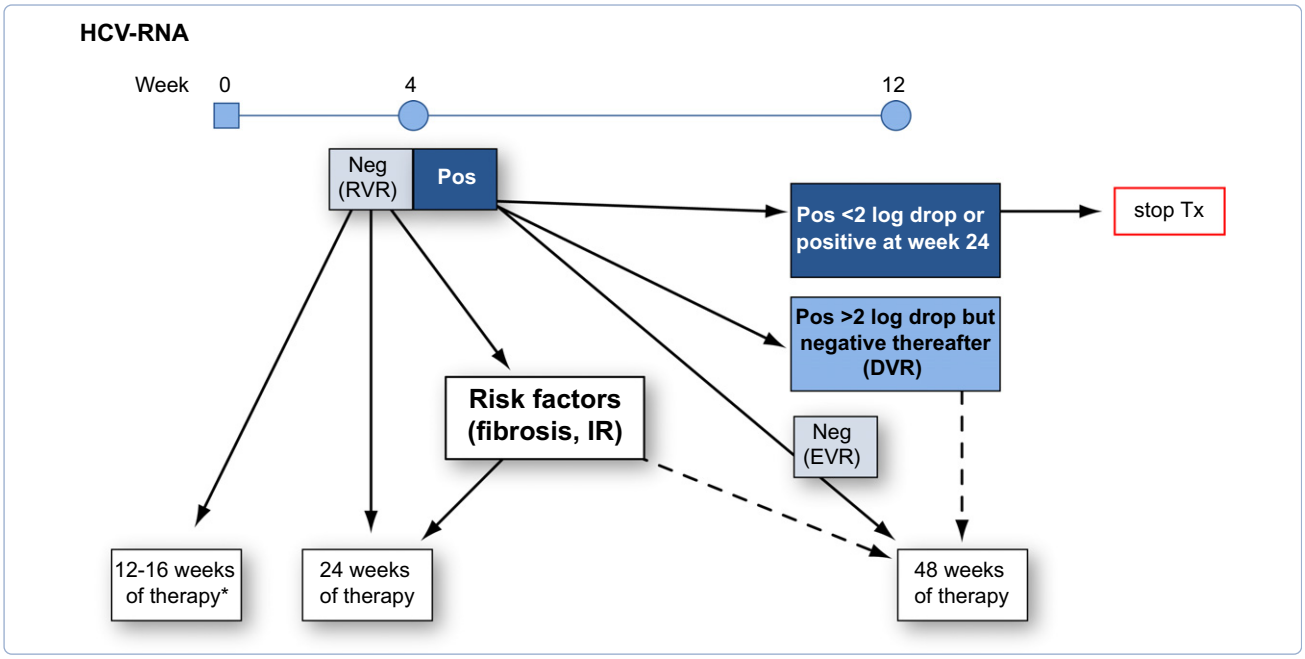


Fig. 3. Response-guided therapy in patients with genotypes 2 and 3 (applies also to genotypes 5 and 6, excluding 12–16 weeks, at a C2 grade of evidence).
*Marginally less effective due to higher relapse rates, especially for G3 with high viral load.

4.11. Measures to improve treatment success rates

Simple measures should be taken in order to improve success rates, as they have been shown to be associated with significantly higher SVR rates.

4.11.1. Treatment adherence

Full adherence to both pegylated IFN-α and ribavirin is associated with improved SVR rates [57]. It is recommended that any dose reductions are reviewed and a full dose reinstated as soon as possible to attain and sustain maximum exposure to each drug [110]. Factors influencing adherence have been reviewed and addressed in individual studies. These have demonstrated that homelessness, active injection drug use, or ongoing opiate substitution therapy can each be addressed to result in SVR rates equivalent to those seen in registration trials [111–113].

4.11.2. Supportive care

Before starting antiviral therapy, patients must be instructed about the schedule and the side effects to be expected during treatment. Patients should also be instructed about the preventive and therapeutic measures to ameliorate these side effects, for e.g. by using antipyretics, analgetics, or antidepressants (see below). Regular follow-up visits must be scheduled so that treatment progress and management issues regarding side effects can be discussed. Easy access to physicians or specialized nursing staff in case of side effects should be facilitated in order to reduce discontinuation rates to a minimum. Patient recall procedures in cases of missed appointments should be instituted.

4.11.3. Correction of cofactors

Body weight. Body weight (BMI) adversely influences the response to pegylated IFN-α and ribavirin, even after dose adjustment for IFN and ribavirin [114]. Body weight reduction prior to therapy is recommended and has been associated with better SVR rates.

Alcohol consumption. Since regular alcohol consumption leads to accelerated fibrosis progression and possibly reduced response to antiviral therapy, it is important to assure that patients abstain from regular alcohol consumption. If patients cannot abstain from regular alcohol consumption, treatment for alcohol dependence should be attempted before the initiation of antiviral therapy, and additional support should be given to them during antiviral therapy so they adhere to a full course of therapy [115]. Patients should be counseled to either completely abstain from alcohol consumption during antiviral therapy or, less preferably, to at least reduce alcohol consumption to occasional small amounts.

Insulin resistance. Insulin resistance is associated with fibrosis progression in chronic hepatitis C and an increased HOMA index has been shown to be an independent predictor of treatment failure in patients treated with pegylated IFN-α and ribavirin [116]. No prospective trials of relevant size have been published to date to prove the efficacy of a therapeutic intervention aimed at improving insulin resistance in SVR. Thus, it is premature to issue any recommendation as to the use of drugs that reduce insulin resistance and proper trials need to be performed.

4.11.4. Supportive therapy

Growth factors. The use of growth factors has been suggested to be helpful in limiting treatment dose reductions.

Recombinant erythropoietin can be used to maintain or improve hemoglobin levels in order to avoid ribavirin dose reductions or interruptions, which have been shown to be associated with higher treatment failure rates. Although no prospective trials have been designed to date to definitely demonstrate that the use of erythropoietin has a positive impact on SVR, it is broadly used worldwide to maintain high doses of ribavirin and improve patients' well being [117]. Erythropoietin can be administered when the hemoglobin level falls below 10 g/dl. The hemoglobin level should be re-assessed 2 weeks after the initiation of erythropoietin therapy. At this time point, the erythropoietin dose should be reduced if the increase in hemoglobin is more than 1 g/dl and stopped if the hemoglobin level has risen to over 12 g/dl. The hemoglobin level should be re-assessed 4 weeks later. The dose should be reduced if the hemoglobin increase is more than 2 g/dl compared to 4 weeks earlier, and erythropoietin should be stopped if the hemoglobin level is higher than 12 g/dl. In this case, erythropoietin therapy can be re-started at 50% of the initial dose if the hemoglobin level falls again below 12 g/dl. If the hemoglobin level increase is less than 1 g/dl at 4 weeks of administration and no other cause of anemia is found, the erythropoietin dose can be increased.

There is no clear evidence indicating that neutropenia during pegylated IFN-α and ribavirin therapy, a common event in cirrhotic patients, has an adverse effect. In addition, there is no evidence from prospective trials that the use of granulocyte colony-stimulating factor (G-CSF) reduces the rate of infections and/or improves SVR rates. Even though G-CSF is used in some countries in Europe [117] as soon as the neutrophil count drops below 750–500/mm^3, there is insufficient evidence to recommend this practice as standard treatment.

A thrombopoetin receptor agonist has been shown to be able to increase platelet counts prior to therapy in thrombocytopenic patients with HCV-related cirrhosis [118]. Discontinuation rates due to thrombocytopenia are rare and patients with low platelet counts can generally be initiated on pegylated IFN-α and ribavirin therapy without an increase in major bleeding episodes. Until SVR can be shown to be improved by improving platelet counts, no recommendations can be made as to the use of thrombopoiesis-stimulating agents. The risk of portal vein thrombosis during treatment with eltrombag, a thrombopoetin receptor agonist-stimulating agent, needs to be considered [119].

Antidepressants. Depression has a severe adverse impact on health-related quality of life during pegylated IFN-α and ribavirin therapy and was the most frequent reason for treatment discontinuations in the pivotal trials. Patients with a history and/or signs of depression should be seen by a psychiatrist before therapy initiation in order to assess the risk and evaluate potential contra-indications. They should be followed-up thereafter if needed. Antidepressant therapy should be initiated during therapy if felt appropriate, and appropriate follow-up is required to decide whether treatment interruption is needed. Preventive antidepressant therapy can be discussed as its efficacy in reducing the incidence of depression during treatment has been reported, without any impact on the SVR [120]. Hypersensitivity with irritability and anxiety resulting from IFN-induced sleep deprivation should not be confounded with depression and

should be adequately treated with anxiolytics rather than sleeping pills or antidepressants [121].

Recommendations

(1) Full adherence to both pegylated IFN-α and ribavirin schedules should be the aim in order to optimize SVR rates (A1).
(2) Body weight adversely influences the response to pegylated IFN-α and ribavirin (A2). Body weight reduction in overweight patients prior to therapy may increase likelihood of SVR (C2).
(3) Insulin resistance is associated with treatment failure (B2). Insulin sensitizers have no proven efficacy in improving SVR rates in insulin-resistant patients (C2).
(4) Patients should be counseled to abstain from alcohol during antiviral therapy (C1).
(5) Recombinant erythropoietin (EPO) can be administered when the hemoglobin level falls below 10 g/dl in order to avoid ribavirin dose reduction or discontinuation (C2).
(6) There is no evidence that neutropenia during pegylated IFN-α and ribavirin therapy is associated with more frequent infection episodes (C1), or that the use of granulocyte colony-stimulating factor (G-CSF) reduces the rate of infections and/or improves SVR rates (B1).
(7) Patients with a history and/or signs of depression should be seen by a psychiatrist before therapy (C2). Patients who develop depression during therapy should be treated with antidepressants. Preventive antidepressant therapy in selected subjects may reduce the incidence of depression during treatment, without any impact on the SVR (B2).

4.12. Post-treatment follow-up of patients who achieve an SVR

Non-cirrhotic patients who achieve an SVR should be retested for ALT and HCV RNA at 48 weeks post-treatment and one year later. If ALT is still normal and HCV RNA is still not detected, the patient can be discharged as cured. As hypothyroidism may occur after stopping therapy, TSH and thyroxine levels should also be assessed 1 year after treatment. In addition, cirrhotic patients must remain under surveillance for esophageal varices every 1–2 years and HCC every 6 months by means of ultrasonography and α-fetoprotein. HCV RNA need not be retested.

Recommendations

(1) Non-cirrhotic patients with SVR should be retested for ALT and HCV RNA at 48 and 96 weeks post-treatment, then discharged if ALT is normal and HCV RNA negative (C2).
(2) In addition to the above, cirrhotic patients with SVR should undergo surveillance for esophageal varices every 1–2 years and HCC every 6 months by means of ultrasonography and α-fetoprotein (B1).

4.13. Re-treatment of non-sustained virological responders to pegylated IFN-α and ribavirin

Non-sustained virological responders to a prior course of pegylated IFN-α and ribavirin that have been infected with HCV genotype 1 have only a small likelihood of achieving an SVR; when re-treated with the same drugs at the same doses, the likelihood does not exceed 10–15% for non-responders and 30–40% for relapsers. Hence, these patients should have re-treatment deferred and be re-evaluated for treatment with direct acting antivirals (e.g. HCV protease inhibitors) in combination with pegylated IFN-α and ribavirin as soon as these drugs become available.

The first generation protease inhibitors i.e. telaprevir and bocepreivr, are not efficacious and will not be licensed for use in non -1 genotypes. Non-genotype 1 non-responder patients can thus be re-treated with pegylated IFN-α and ribavirin if they have an urgent indication for therapy, and/or if there is evidence of inadequate exposure to either pegylated IFN-α or ribavirin due to dose adjustments or poor adherence during the first course of therapy. Longer re-treatment durations (48 weeks for genotypes 2 and 3, 72 weeks for genotype 4 patients) might be advisable, especially in patients with DVR and relapse in the first cycle of treatment [36,56,62,122]. With the current clinical development of a number of new drugs for the treatment of chronic HCV infection, it is recommended that, whenever possible, patients who failed to respond to a first course of pegylated IFN-α and ribavirin should be included in clinical trials with these new drugs.

Maintenance therapy with a low dose of pegylated IFN-α is generally not recommended as it has shown no general efficacy in preventing chronic hepatitis C complications in the long-term [123]. Recent data from an extended analysis of the HALT-C cohort suggest that long-term peginterferon therapy slightly reduces the incidence of HCC among patients with cirrhosis who received peginterferon, regardless of whether SVR was achieved [124]. However, considering the marginal beneficial effect and the side effects and costs of peginterferon, the utility of peginterferon maintenance therapy is doubtful.

Recommendations

(1) Patients infected with HCV genotype 1 who failed to eradicate HCV in prior therapy with pegylated IFN-α and ribavirin should generally not be re-treated with the same drug regimen (A2). They may be considered for re-treatment with the triple combination of pegylated IFN-α, ribavirin, and a protease inhibitor when available.
(2) Non-sustained virological responders to a prior course of pegylated IFN-α and ribavirin can be re-treated with pegylated IFN-α and ribavirin if they have an urgent indication for therapy, and/or if there is evidence of inadequate exposure to either pegylated IFN-α or ribavirin due to dose adjustments or poor adherence during the first course of therapy (C2).
(3) Patients infected with HCV genotypes other than 1 who failed on prior therapy with IFN-α with or without ribavirin can be re-treated with pegylated IFN-α and ribavirin as no other options will be available soon (B2).
(4) Maintenance therapy with a low dose of pegylated IFN-α is not recommended (A1).

4.14. Treatment of patients with severe liver disease

4.14.1. Compensated cirrhosis

Patients with compensated cirrhosis must be treated in the absence of contra-indications, in order to prevent the complica-

tions of chronic HCV infection that occur exclusively in this group in the short- to mid-term. Indeed, large cohort studies and meta-analyses have shown that an SVR in patients with advanced fibrosis is associated with a significant decreased incidence of clinical decompensation and HCC. However, the SVR rates with pegylated IFN-α and ribavirin are lower in patients with advanced fibrosis or cirrhosis than in patients with mild to moderate fibrosis. Thus, it may also be justified to wait for the approval of triple therapies with protease inhibitors (genotype 1) if their local availability is anticipated within a few months.

Assiduous monitoring and management of side-effects is required in this group of patients, who are generally older and have a lower tolerance than patients with less advanced liver disease. Due to portal hypertension and hypersplenism, leukocyte and platelet counts at baseline may be low in cirrhotic patients. Hematological side effects are more frequent in cirrhotic than in non-cirrhotic patients [125], and may contraindicate therapy. Growth factors might be useful in this group.

Irrespective of the achievement of an SVR, patients with cirrhosis should undergo regular surveillance for the occurrence of HCC and for portal hypertension, as the risk of complications is decreased but not abolished when HCV infection has been eradicated.

Recommendations

(1) Patients with compensated cirrhosis should be treated, in the absence of contraindications, in order to prevent short- to mid-term complications (A1).
(2) Assiduous monitoring and management of side-effects, especially those linked to portal hypertension and hypersplenism, is required. Growth factors are particularly useful in this group (C2).
(3) Patients with cirrhosis should undergo regular surveillance for HCC, irrespective of SVR (B1).

4.14.2. Patients with an indication for liver transplantation

Liver transplantation is the treatment of choice for patients with end-stage liver disease. However, hepatitis C recurrence due to graft infection is universal after transplantation [126]. Antiviral therapy in patients awaiting transplantation prevents graft infection if an SVR is achieved [126–128]. More than half of the patients have contraindications for the use of pegylated IFN-α and ribavirin, and the results of therapy are generally poor in this group of individuals with advanced or decompensated liver disease. Antiviral therapy is indicated in patients with conserved liver function (Child–Pugh A) in whom the indication for transplantation is HCC. In patients with Child–Pugh B cirrhosis, antiviral therapy may be offered on an individual basis in experienced centers, preferentially in patients with predictors of good response, such as patients infected with HCV genotypes 2 or 3, or patients with a low baseline HCV RNA level. Patients with Child–Pugh C cirrhosis should not be treated with the SoC, due to a high risk of life-threatening complications [126–129].

For those individuals with severe liver disease that can be treated before transplantation, antiviral therapy should be started at the time of enlistment, with the goal of achieving an SVR [128], or while awaiting transplantation in order to achieve HCV-RNA clearance at the time of transplantation [126, 127,129]. Approximately 75% of patients rendered HCV RNA negative at the time of transplantation remain negative post-transplantation. Treatment can be started at low doses of pegylated IFN-α and ribavirin, following a low accelerated dose regimen, or if possible, at full doses. In the latter case, dose reductions and treatment interruptions are required in more than 50% of cases. Hematological adverse events (anemia, neutropenia, and thrombocytopenia) are particularly frequent in patients with end-stage liver disease because of portal hypertension. Treatment, therefore, requires close monitoring and dose modifications. The use of growth factors (erythropoietin and G-CSF) might be helpful to control hematological side effects.

Recommendations

(1) In patients awaiting transplantation, antiviral therapy, when feasible, prevents graft re-infection if an SVR is achieved (B1). Many patients have contra-indications to treatment and the results of therapy are generally poor in this group of individuals with very advanced liver disease (B1).
(2) Antiviral therapy might be started at the time of enlistment or while awaiting LT, with the goal of achieving an SVR or HCV-RNA clearance before LT (C2).
(3) Antiviral therapy is indicated in patients with conserved liver function (Child–Pugh A) in whom the indication for transplantation is HCC (B2).
(4) In patients with Child–Pugh B cirrhosis, antiviral therapy is offered on an individual basis in experienced centers, preferentially in patients with predictors of good response (C2). Norfloxacin prophylaxis should be given if ascites is present (C2).
(5) Patients with Child–Pugh C cirrhosis should not be treated with the current antiviral regimen, due to a high risk of life-threatening complications (C1).
(6) Treatment can be started at low doses of pegylated IFN-α and ribavirin, following a low accelerated dose regimen, or at full doses. In the latter case, dose reductions and treatment interruptions are required in more than 50% of cases (C2).

4.14.3. Post-liver transplantation recurrence

HCV infection recurrence is universal in patients with detectable HCV RNA at the time of liver transplantation [126]. The course of HCV-related liver disease is accelerated in liver transplant recipients and approximately one third of them develop cirrhosis within 5 years following transplantation [130,131]. Successful therapy has been shown to have a positive impact on both graft and patient survival [132].

Patients with post-transplant recurrence of HCV infection should initiate therapy once chronic hepatitis is established and histologically proven; these patients generally have a better background for therapy than at the acute stage of re-infection and related hepatitis, i.e. lowered immunosuppression, an improved clinical status ensuring better tolerability, and a lower risk of triggering graft rejection upon IFN-based therapy. The presence of significant fibrosis or portal hypertension one year after transplantation is predictive of rapid disease progression and graft loss, and urgently indicates antiviral treatment [133,134]. In patients with less advanced disease, such as those with fibrosis restricted to the portal tract and no portal hypertension, indications for therapy must be weighed against the

likelihood of a sustained viral eradication and the risk of complications due to the use of pegylated IFN-α and ribavirin. Nevertheless, these patients have a better chance of an SVR than those with more advanced disease.

The likelihood of an SVR in the post-transplant setting is on the order of 30% overall, with better response rates in patients infected with HCV genotypes 2 or 3 than genotype 1 [132,135,136]. As renal insufficiency is common in liver transplant recipients, ribavirin doses need to be adjusted accordingly. The relatively low efficacy of pegylated IFN-α and ribavirin therapy in HCV-infected transplant recipients is at least partly due to the high incidence of side effects that result in frequent dose adjustments and treatment interruptions. Anemia is the most common cause of treatment interruption in this setting (10–40% of the patients) [135,136]. Therefore, the use of erythropoietin can be recommended in this setting. Graft rejection is rare but may occur during IFN-α treatment. A liver biopsy should be performed whenever liver tests worsen during the course of antiviral therapy to diagnose it and guide treatment decision. There is no evidence for the benefit of low-dose pegylated IFN-α maintenance therapy in patients who do not achieve an SVR.

Recommendations

(1) Patients with post-transplant recurrence of HCV infection should initiate therapy once chronic hepatitis is established and histologically proven (B2). Significant fibrosis or portal hypertension one year after transplantation predicts rapid disease progression and graft loss and indicates urgent antiviral treatment (B2).
(2) There is no evidence of benefit from low-dose pegylated IFN-α maintenance therapy in patients who do not achieve an SVR (C2).
(3) Graft rejection is rare but may occur during IFN-α treatment (C2). A liver biopsy should be performed whenever liver tests worsen upon antiviral therapy to guide treatment decisions (C2).

4.15. Treatment of special groups

4.15.1. HIV coinfection

Progression of liver disease is accelerated in patients with HIV-HCV co-infection, in particular those with a low CD4-positive cell count and impaired immune function. For this reason, early antiretroviral therapy should be considered in patients with HIV-HCV co-infection [137]. If the patient has severe immunodeficiency, with a CD4-positive cell count <200 cells/μl, the CD4 count should be improved using highly active antiretroviral therapy prior to commencing anti-HCV treatment. During pegylated IFN-α and ribavirin treatment, didanosine is contraindicated. Stavudine and zidovudine should be avoided, while the role of abacavir remains debated. The severity of liver disease must be assessed prior to therapy by means of a liver biopsy or by non-invasive assessment (serological tests or transient elastography) [138].

Indications for HCV treatment are identical to those in patients with HCV monoinfection [139]. The same pegylated IFN-α regimen should be used in HIV-co-infected patients as in patients without HIV infection. Weight-based doses of ribavirin (15 mg/kg/day) should be used, whatever the HCV genotype [138]. Monitoring of viral kinetics on treatment should be performed and the patients should be treated according to their virological response at weeks 4 and 12. Rates of SVR are generally lower than in monoinfected patients, proportionally to HCV genotype [138]. Patients infected with genotypes 2 or 3 with low baseline HCV RNA level (<400,000 IU/ml) and mild fibrosis who achieve an RVR may only need 24 weeks of therapy. Other patients need 48 weeks of therapy, and treatment should be extended to 72 weeks in patients who are still HCV RNA-positive at week 12 (DVR), whatever the HCV genotype.

Recommendations

(1) Indications for HCV treatment are identical to those in patients with HCV monoinfection (B2).
(2) The same pegylated IFN-α regimen should be used in HIV-co-infected patients as in patients without HIV infection, but ribavirin should always be weight-based dosed (B2).
(3) Longer treatment duration (72 weeks for genotype 1 and 48 weeks for genotypes 2 and 3) may be needed (B2).

4.15.2. HBV coinfection

In patients with HCV-HBV co-infection, the HBV DNA level is often low or undetectable, although it may fluctuate widely, and HCV is usually the main driver of chronic hepatitis activity. The replicative status of both HBV and HCV should be determined, and hepatitis delta virus infection excluded. When HCV is replicating and causes liver disease, it should be treated with pegylated IFN-α and ribavirin following the same rules as monoinfected patients. The SVR rates in this group are broadly comparable or even higher to those in HCV monoinfected patients [140,141]. There is a potential risk of HBV reactivation during or after HCV clearance [142]. In that case, or if HBV replication is detectable at a significant level, concurrent HBV nucleoside/nucleotide analogue therapy may be indicated. For telbivudine, potentially increased toxicity, related to neuropathy, when used in conjunction with IFN has been reported.

Recommendations

(1) Patients should be treated with pegylated IFN-α and ribavirin, following the same rules as monoinfected patients (B2).
(2) If HBV replicates at significant levels before, during or after HCV clearance, concurrent HBV nucleoside/nucleotide analogue therapy is indicated (C2).

4.15.3. Treatment of patients with comorbidities

Hemodialysis patients. Due to the negative long-term impact of HCV infection after transplantation and to the current lack of treatment options for HCV after kidney transplantation, treatment of hemodialysis patients should be attempted when possible. Ribavirin is cleared by the kidneys. Therefore, hemodialysis patients have been treated with pegylated IFN-α monotherapy at the usual doses [143]. In the absence of ribavirin, SVR rates are substantially lower than in non-dialysis patients. Rates between 30% and 50% of discontinuation of pegylated IFN-α monotherapy are reported. Careful patient selection and side effect management are important. Combination treatment with

pegylated IFN-α and ribavirin might be considered by experienced physicians, with individualized ribavirin dosing of 200 mg/day to 200 mg/every other day and substantial hematopoietic support, as suggested by few preliminary studies. Since PegIFN-alpha2a is cleared through the liver and PegIFN-alpha2b primarily through the kidneys, there could be a theoretical accumulation of PegIFN-alpha2b when used in hemodialysis patients, which could either cause more side effects or an increased efficacy [144,145]. Even though this has not been formally compared, no obvious differences are observed clinically.

Non-hepatic solid organ transplant recipients. HCV infection in kidney transplant recipients is associated with an increased risk of fibrosis progression and liver-related mortality. As cirrhosis is an important predictor of poor post-transplant survival after kidney transplantation, it is advisable to obtain a liver biopsy from all HCV-positive kidney transplant candidates [146]. Treatment of chronic HCV infection with pegylated IFN-α and ribavirin in kidney transplant recipients is associated with a risk of acute or chronic cellular rejection of 30% or more, resulting in graft loss and reduced patient survival. Therefore, pegylated IFN-α and ribavirin therapy has additional risks in these patients, and indications for treatment must be tailored accordingly. Subjects with an indication for kidney transplantation should be treated for hepatitis C prior to transplantation [147].

Data on HCV infection after heart transplantation are scarce and controversial, with studies showing unaltered or decreased survival rates in patients infected with HCV. No studies on the risks and benefits of antiviral therapy are available in these patients and the risk of graft rejection upon IFN-α treatment remains unclear. In this context, treatment of chronic HCV infection in heart transplant recipients cannot be recommended and the indication should be assessed on a case-by-case basis, if HCV infection is life-threatening.

International guidelines list chronic HCV infection as an absolute contraindication to lung transplantation [148]. Treatment of lung transplant candidates before transplantation has been recommended by some authors, but there is limited experience with this approach. No data are available on the impact of HCV infection and its treatment after pancreas or small bowel transplantation.

Alcohol abuse. Chronic alcohol consumption in patients with chronic hepatitis C is associated with an accelerated fibrosis progression, a higher frequency of cirrhosis, and a higher incidence of HCC [149]. SVR rates are lower in patients abusing alcohol [115]. Nevertheless, at least moderate alcohol consumption is found in two-thirds of patients with chronic hepatitis C and only half of them discontinue alcohol consumption upon counseling and treatment initiation. The impact on response to SoC is unclear. Patients with alcohol consumption should not be excluded from treatment but should receive counseling to stop their consumption and additional support to improve adherence during therapy.

Drug abuse. Little data are available on the treatment of active drug users, due to the widely accepted notion that patients should be drug-free or on stable substitution therapy for at least 6–12 months. No general recommendation for treatment of active drug users can be made. An individualized approach after evaluation and close monitoring by an experienced multidisciplinary team of hepatologists and addictologists is recommended [150].

Patients on stable maintenance substitution. Drug addicts on methadone substitution therapy do not seem to have lower SVR rates upon pegylated IFN-α and ribavirin therapy. However, discontinuation during the first 8 weeks of therapy appears to be slightly more frequent [111]. In these patients, antiviral therapy should be instituted after careful individual evaluation by an interdisciplinary team of hepatologists and addictologists. Close monitoring and support for adherence and mental health are recommended.

Hemoglobinopathies. The most frequent hemoglobinopathy associated with chronic hepatitis C is thalassemia major, which requires frequent blood transfusions and is prevalent in countries where blood supply screening may be less stringent than in industrialized areas. In the few published clinical trials, these patients had a higher incidence of anemia and iron accumulation on standard combination of pegylated IFN-α and ribavirin. Therefore, they can be treated with standard combination therapy, but these complications should be carefully managed with growth factors, blood transfusions, and iron chelation therapy when needed [151].

Chronic HCV infection is frequent in individuals with sickle cell anemia, as a consequence of the number of blood transfusions received. No trials with antiviral therapy have been published in this population. Individual cases have been successfully treated with the combination of pegylated IFN-α and ribavirin.

Recommendations

(1) Patients on hemodialysis can safely be treated with PegIFN-monotherapy (A2). Combination treatment with individualized doses of ribavirin can be considered in selected patients (C2).
(2) Patients with HCV and end stage renal disease scheduled for kidney transplantation should undergo antiviral therapy prior to kidney transplantation due to the increased risk of acute transplant rejection (B2).
(3) Regular alcohol consumption should be strongly discouraged (A1).
(4) Treatment of patients with active illicit drug abuse has to be decided on an individual basis and should be carried out in an interdisciplinary team together with addictologists (C2).
(5) Treatment of patients with active illicit drug abuse on stable maintenance substitution treatment can be safely performed in an interdisciplinary team involving addictologists and yields only slightly reduced SVR-rates compared to conventional HCV-patients (B2).
(6) Patients with hemoglobinopathies can be treated with combination therapy but need careful monitoring for hematologic side effects (C2).

4.16. Follow-up of untreated patients and of non-sustained responders

Untreated patients with chronic hepatitis C and those who failed to respond to previous cycles of treatment should be regularly followed. Previous guidelines recommended performing a liver biopsy every 3–5 years. With non-invasive methods, more frequent screening can be performed. Thus, untreated patients should be assessed every 1–2 years with a non-invasive method. Patients with cirrhosis should undergo specific screening for HCC every 6 months.

Recommendations

(1) Untreated patients with chronic hepatitis C and non-sustained responders should be regularly followed (C2).
(2) HCC screening must be continued indefinitely in patients with cirrhosis (A2).

4.17. Treatment of acute hepatitis C

Most patients with acute hepatitis C are asymptomatic, but a high rate of chronicity is expected (50–90%). Symptomatic disease, female gender, a young age, clearance of HCV RNA within four weeks after the onset of clinical symptoms, and genetic polymorphisms in the region upstream of the IL28B gene have been associated with spontaneous viral clearance, but none of these parameters accurately predicts spontaneous resolution at the individual level.

Early identification of acute hepatitis C is important, but may be difficult as the disease may be relatively silent. Patients with acute hepatitis C should be considered for antiviral therapy in order to prevent progression to chronic hepatitis C. High SVR rates (up to 90% or even higher) have been reported with pegylated IFN-α monotherapy, essentially in a series of symptomatic patients, regardless of the HCV genotype. Early treatment of these individuals is usually advisable, but no consensus exists: In those who do not appear to be convalescing 2–4 months after onset of the disease, antiviral treatment (see below) should be considered, as a high percentage of patients (>80–90%) may respond, and the risk of chronic disease is high. Combination therapy with ribavirin does not increase the SVR rate in this setting but may be considered in those patients where the differential diagnosis of acute vs. chronic hepatitis is uncertain [4,8,152–156]. The most important determinant of lack of response in non-adherence is in patients with acute hepatitis C.

It has also been suggested to follow these patients with HCV RNA quantification every 4 weeks and to treat only those still positive at 12 weeks after initial presentation [157]. Some clinicians may prefer to start treatment earlier if the HCV RNA is high and not declining. The usual treatment of acute hepatitis C should be based on pegylated IFN-α monotherapy, i.e. either pegylated IFN-α2a, 180 μg/week, or pegylated IFN-α2b, 1.5 μg/kg/week, for 24 weeks. There is currently no indication for administering IFN-α as post-exposure prophylaxis in the absence of documented HCV transmission.

Recommendations

(1) Pegylated IFN-α monotherapy (pegylated IFN-α2a, 180 μg/week or pegylated IFN-α2b, 1.5 μg/kg/week, for 24 weeks) is recommended in patients with acute hepatitis C and obtains viral eradication in >90% of patients (B2).
(2) Patients failing to respond should be re-treated according to the standard of care for chronic hepatitis C (C2).

4.18. Perspective of triple therapy with PEG-interferon, ribavirin, and protease inhibitors

Important progress has been made in the development of new treatments, in particular new specific inhibitors or direct antiviral agents active against hepatitis C. A large number of trials investigating NS3 protease inhibitors, NS5A and NS5B polymerase inhibitors, cyclophilin inhibitors, new forms of interferon, derivatives of ribavirin, and therapeutic vaccines are in progress. Studies are mostly directed at patients infected by HCV genotype 1 [158].

Phase III clinical trials combining pegylated IFN-α, ribavirin, and a direct acting antiviral of the HCV protease inhibitor family (telaprevir or boceprevir) have been completed. These data will likely lead to the approval of a triple therapy in patients infected with HCV genotype 1 who are treatment-naïve or had non-response to a prior course of pegylated IFN-α and ribavirin. The pivotal trials with telaprevir and boceprevir have confirmed that a significantly higher proportion of naïve and non-responder patients with genotype 1 infection have an SVR, with response-guided therapy. In a proportion of patients with satisfactory early responses, treatment can be significantly shortened [41–44]. Telaprevir is adminstered three times daily. Boceprevir is administered three times daily after a 4 week lead-in-phase of PEG-IFN-α plus ribavirin alone. In treatment-naïve patients SVR rates were 27–31% higher when receiving triple therapy. Response-guided treatment is utilized; 24 weeks of therapy is given for patients who become HCV RNA negative at weeks 4 and 12 (eRVR) (telaprevir) or HCV RNA negative from treatment week 8 through 24 (boceprevir), 48 weeks of treatment is required for non-eRVR patients. Shorter treatment is likely to be possible in 50–66% of patients. Previous relapse patients show very high SVR rates of 75%-86%, while response rates are lower for partial responder (>2 log decline in HCV RNA at 12 weeks of prior therapy) (50–60%) and previous null-responder patients (33%, data only for telaprevir) [159]. Factors associated with response to triple therapy remain to be determined: advanced fibrosis and African-American ethnicity has been identified as an independent negative predictor of response.

The present guidelines will be updated when these combinations are approved. In patients infected with HCV genotypes other than 1, the current guidelines will still apply.

Recommendations

(1) New direct acting antiviral agents should be used only according to the package label.
(2) Potential challenges should be considered when using HCV protease inhibitors in combination with pegylated IFNa and ribavirin:
  – Rapid emergence of drug resistance in particular in previous non-responder patients, subjects not fully adherent to therapy, and individuals not being able to tolerate optimal doses of PEG-IFNa and ribavirin treatment.
  – More strict and frequent monitoring of serum HCV RNA.
  – Lower response rates to triple therapy in patients with advanced liver fibrosis.
  – Adherence to recommended stopping rules for the antiviral agent and/or the entire treatment regimen.
  – Additional side effects associated with protease inhibitor treatment.

Disclosures

Antonio Craxi has received research support, lecture fees and took part in clinical trials for Roche, MSD, Siemens, and Abbott.

Geoffrey Dusheiko has received research support, lecture fees and took part in clinical trials for Vertex, Gilead, Novartis, Novartis Genome Sciences, Pharmasett, Roche, MSD, Tibotec, Abbott, Boehringer Ingelheim, BMS, and Pfizer.

Robert Flisiak has received research support, lecture fees from Roche, MSD, BMS, Novartis, Debiopharm, Pfizer, and Gilead.

Xavier Forns has received research support and took part in clinical trials for Roche and Schering-Plough/MSD, and Janssen.

Markus Peck-Radosavljevic has received research support, lecture fees from MSD, and Roche.

Jean-Michel Pawlotsky has received research support, lecture fees and took part in clinical trials for Abbott, Achillion, Anadys, Biotica, Boehringer-Ingelheim, Bristol-Myers Squibb, DebioPharm, Gilead, Glaxo-SmithKline, Idenix, Janssen-Cilag/Tibotec, Madaus Rottapharm, Merck/Schering-Plough, Novartis, Pfizer, Pharmasset, Roche, and Vertex.

William Rosenberg has received research support, lecture fees and took part in clinical trials Roche, Gilead, MSD, Boehringer-Inghelheim, Siemens. He is a stockholder of iQUR LTD.

Christoph Sarrazin has received research support, lecture fees and took part in clinical trials for Roche, MSD, Siemens, and Abbott.

Heiner Wedemeyer has received research support, lecture fees and took part in clinical trials for Roche, MSD, Novartis, Gilead, BMS, Abbott, Biolex, and Johnson & Johnson.

Ira Jacobson has received research support, lecture fees and took part in clinical trials for MSD, Novartis, Gilead, BMS, Abbott, Vertex, Tibotec, Pfizer, Pharmasset, Boehringer-Inghelheim, GlobeImmune, Anadys, Zymogenetics, Sanofi-aventis, Glaxo-SmithKline, Achillion, Biolex, Human Genome Sciences, and Roche/Genentech. He is on a speaker's bureau for MSD, Gilead, MSD, Roche/Genentech.

Acknowledgments

The contributors thank Dr. Svenja Hardtke (Hannover Medical School, Germany) and Dr. Sonia Guimil and Dr. Adam Swetloff (Journal of Hepatology) for editorial assistance.

References

[1] Lavanchy D. The global burden of hepatitis C. Liver Int 2009;29:74–81.
[2] Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. Lancet Infect Dis 2005;5:558–567.
[3] Esteban JI, Sauleda S, Quer J. The changing epidemiology of hepatitis C virus infection in Europe. J Hepatol 2008;48:148–162.
[4] Kamal SM, Nasser IA. Hepatitis C genotype 4: what we know and what we don't yet know. Hepatology 2008;47:1371–1383.
[5] van de Laar TJW, Matthews GV, Prins M, Danta M. Acute hepatitis C in HIV-infected men who have sex with men: an emerging sexually transmitted infection. AIDS 2010;24:1799–1812.
[6] Simmonds P, Bukh J, Combet C, Deleage G, Enomoto N, Feinstone S, et al. Consensus proposals for a unified system of nomenclature of hepatitis C virus genotypes. Hepatology 2005;42:962–973.
[7] Antaki N, Craxi A, Kamal S, Moucari R, Van der Merwe S, Haffar S, et al. The neglected hepatitis C virus genotypes 4, 5 and 6: an international consensus report. Liver Int 2010;30:342–355.
[8] Santantonio T, Wiegand J, Gerlach JT. Acute hepatitis C: current status and remaining challenges. J Hepatol 2008;49:625–633.
[9] Wiegand J, Deterding K, Cornberg M, Wedemeyer H. Treatment of acute hepatitis C: the success of monotherapy with (pegylated) interferon alpha. J Antimicrob Chemother 2008;62:860–865.
[10] Afdhal NH. The natural history of hepatitis C. Semin Liver Dis 2004;24: 3–8.
[11] Thompson CJ, Rogers G, Hewson P, Wright D, Anderson R, Cramp M, et al. Surveillance of cirrhosis for hepatocellular carcinoma: systematic review and economic analysis. Health Technol Assess 2007;11:1–206.
[12] Yang JD, Roberts LR. Hepatocellular carcinoma: a global view. Nat Rev Gastroenterol Hepatol 2010;7:448–458.
[13] Bartosch B, Thimme R, Blum HE, Zoulim F. Hepatitis C virus-induced hepatocarcinogenesis. J Hepatol 2009;51:810–820.
[14] Deuffic-Burban S, Deltenre P, Louvet A, Canva V, Dharancy S, Hollebecque A, et al. Impact of viral eradication on mortality related to hepatitis C: a modeling approach in France. J Hepatol 2008;49:175–183.
[15] Deuffic-Burban S, Babany G, Lonjon-Domanec I, Deltenre P, Canva-Delcambre V, Dharancy S, et al. Impact of pegylated interferon and ribavirin on morbidity and mortality in patients with chronic hepatitis C and normal aminotransferases in France. Hepatology 2009;50:1351–1359.
[16] Zignego AL, Craxi A. Extrahepatic manifestations of hepatitis C virus infection. Clin Liver Dis 2008;12:611–636, ix.
[17] Chevaliez S, Pawlotsky JM. Diagnosis and management of chronic viral hepatitis: antigens, antibodies and viral genomes. Best Pract Res Clin Gastroenterol 2008;22:1031–1048.
[18] Vermehren J, Kau A, Gartner BC, Gobel R, Zeuzem S, Sarrazin C. Differences between two real-time PCR-based hepatitis C virus (HCV) assays (RealTime HCV and Cobas AmpliPrep/Cobas TaqMan) and one signal amplification assay (Versant HCV RNA 3.0) for RNA detection and quantification. J Clin Microbiol 2008;46:3880–3891.
[19] Chevaliez S, Bouvier-Alias M, Pawlotsky JM. Performance of the Abbott Real-Time PCR assay using m2000(sp) and m2000(rt) for hepatitis C virus RNA quantification. J Clin Microbiol 2009;47:1726–1732.
[20] Fytili P, Tiemann C, Wang C, Schulz S, Schaffer S, Manns MP, et al. Frequency of very low HCV viremia detected by a highly sensitive HCV-RNA assay. J Clin Virol 2007;39:308–311.
[21] Chevaliez S, Bouvier-Alias M, Brillet R, Pawlotsky JM. Hepatitis C virus (HCV) genotype 1 subtype identification in new HCV drug development and future clinical practice. PLoS One 2009;4:e8209.
[22] Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, et al. Histological grading and staging of chronic hepatitis. J Hepatol 1995;22:696–699.
[23] Desmet VJ, Gerber M, Hoofnagle JH, Manns M, Scheuer PJ. Classification of chronic hepatitis: diagnosis, grading and staging. Hepatology 1994;19:1513–1520.
[24] Poynard T, Ngo Y, Munteanu M, Thabut D, Massard J, Moussalli J, et al. Biomarkers of liver injury for hepatitis clinical trials: a meta-analysis of longitudinal studies. Antiviral Therapy 2010;15:617–631.
[25] Castera L. Transient elastography and other noninvasive tests to assess hepatic fibrosis in patients with viral hepatitis. J Viral Hepat 2009;16:300–314.
[26] Ge DL, Fellay J, Thompson AJ, Simon JS, Shianna KV, Urban TJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature 2009;461:399–401.
[27] Tanaka Y, Nishida N, Sugiyama M, Kurosaki M, Matsuura K, Sakamoto N, et al. Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. Nat Genet 2009;41:1105–1109.
[28] Suppiah V, Moldovan M, Ahlenstiel G, Berg T, Weltman M, Abate ML, et al. IL28B is associated with response to chronic hepatitis C interferon-alpha and ribavirin therapy. Nat Genet 2009;41:1100–1174.
[29] Rauch A, Kutalik Z, Descombes P, Cai T, Di Iulio J, Mueller T, et al. Genetic variation in IL28B is associated with chronic hepatitis C and treatment failure: a genome-wide association study. Gastroenterology 2010;138:1338–1345, 1345.e1–7.
[30] Thomas DL, Thio CL, Martin MP, Qi Y, Ge D, O'hUigin C, et al. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. Nature 2009;461:798–801.
[31] Tillmann HL, Thompson AJ, Patel K, Wiese M, Tenckhoff H, Nischalke HD, et al. A polymorphism near IL28B is associated with spontaneous clearance of acute hepatitis C virus and jaundice. Gastroenterology 2010;139: 1586–1592.
[32] Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 2009;49:1335–1374.

[33] McCaughan GW. Asian Pacific Association for the Study of the Liver consensus statements on the diagnosis, management and treatment of hepatitis C virus infection. J Gastroenterol Hepatol 2007;22: 615–633.

[34] de Bruijne J, Buster EHCJ, Gelderblom HC, Brouwer JT, de Knegt RJ, van Erpecum KJ, et al. Treatment of chronic hepatitis C virus infection – Dutch national guidelines. Netherlands J Med 2008;66:311–322.

[35] Italian Association for the study of the liver, Italian Society of infectious td, Italian Society for the study of sexually transmitted diseases. Practice guidelines for the treatment of hepatits C: recommendations from AISF/SIMIT/SIMAST. Dig Liver Dis 2010;42:81–91.

[36] Sarrazin C, Berg T, Ross RS, Schirmacher P, Wedemeyer H, Neumann U, et al. Prophylaxis, diagnosis and therapy of hepatitis C virus (HCV) infection: the German guidelines on the management of HCV infection. Z Gastroenterol 2010;48:289–351.

[37] McHutchison JG, Lawitz EJ, Shiffman ML, Muir AJ, Galler GW, McCone J, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. New Engl J Med 2009;361:580–593.

[38] Rumi MG, Aghemo A, Prati GM, D'Ambrosio R, Donato MF, Soffredini R, et al. Randomized study of peginterferon-alpha 2a plus ribavirin vs peginterferon-alpha 2b plus ribavirin in chronic hepatitis C. Gastroenterology 2010;138:108–115.

[39] Ascione A, De Luca M, Tartaglione MT, Lampasi F, Di Costanzo GG, Lanza AG, et al. Peginterferon alfa-2a plus ribavirin is more effective than peginterferon alfa-2b plus ribavirin for treating chronic hepatitis C virus infection. Gastroenterology 2010;138:116–122.

[40] Shiffman ML. Treatment of hepatitis C in 2011: what can we expect? Curr Gastroenterol Rep 2010;12:70–75.

[41] Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, et al. HCV RESPOND-2 final results: high sustained virologic response among genotype1 previous nonresponders and relapsers to peginterferon/ribavirin when retreated with boceprevir plus PegIntron/ribavirin. Hepatology 2010;52:430A.

[42] Jacobson IM, McHutchison JG, Dusheiko GM, Di Bisceglie AM, Reddy R, Bzowej NH, et al. Telaprevir in combination with peginterferon and ribavirin in genotype 1 HCV treatment-naive patients: final results of Phase 3 ADVANCE study. Hepatology 2010;52:427A.

[43] Poordad F, McCone J, Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al. Boceprevir (BOC) combined with peginterferon alfa-2b/ribavirin (P/R) for treatment-naive patients with hepatitis C (HCV) genotype 1: SPRINT-2 final results. Hepatology 2010;52:402A.

[44] Sherman KE, Flamm SL, Afdhal NH, Nelson DR, Sulkowski MS, Everson GT, et al. Telaprevir in combination with peginterferon alfa2b and ribavirin for 24 or 48 weeks in treatment-naive genotype 1 HCV patients who achieved an extended rapid viral response: final results of Phase 3 ILLUMINATE study. Hepatology 2010;52:401A.

[45] Torresi J, Johnson D, Wedemeyer H. Progress in the development of preventive and therapeutic vaccines for hepatitis C virus. J Hepatol 2011.

[46] Kubitschke A, Bahr MJ, Aslan N, Bader C, Tillmann HL, Sarrazin C, et al. Induction of hepatitis C virus (HCV)-specific T cells by needle stick injury in the absence of HCV-viraemia. Eur J Clin Invest 2007;37:54–64.

[47] Deterding K, Wiegand J, Gruner N, Wedemeyer H. Medical procedures as a risk factor for HCV infection in developed countries: do we neglect a significant problem in medical care? J Hepatol 2008;48: 1019–1020.

[48] Martinez-Bauer E, Forns X, Armelles M, Planas R, Sola R, Vegara M, et al. Hospital admission is a relevant source of hepatitis C virus acquisition in Spain. J. Hepatol 2008:48.

[49] Helbling B, Renner EL, Kammerlander R. Acute hepatitis A in patients with chronic hepatitis C. Ann Intern Med 1999;131:314.

[50] Hasle G, Hoel T, Jensenius M. Mortality of hepatitis A in adults with hepatitis C antibodies. Lancet 1998;351:1888.

[51] Deterding K, Tegtmeyer B, Cornberg M, Hadem J, Potthoff A, Boker KH, et al. Hepatitis A virus infection suppresses hepatitis C virus replication and may lead to clearance of HCV. J Hepatol 2006;45:770–778.

[52] Sagnelli E, Coppola N, Pisaturo M, Masiello A, Tonziello G, Sagnelli C, et al. HBV superinfection in HCV chronic carriers: a disease that is frequently severe but associated with the eradication of HCV. Hepatology 2009;49:1090–1097.

[53] Vento S, Garofano T, Renzini C, Cainelli F, Casali F, Ghironzi G, et al. Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. N Engl J Med 1998;338:286–290.

[54] Effects of mode of delivery and infant feeding on the risk of mother-to-child transmission of hepatitis C virus. European Paediatric Hepatitis C Virus Network. BJOG 2001;108:371–7.

[55] Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. New Engl J Med 2002;347:975–982.

[56] Hadziyannis SJ, Sette H, Morgan TR, Balan V, Diago M, Marcellin P, et al. Peginterferon-alpha 2a and ribavirin combination therapy in chronic hepatitis C – a randomized study of treatment duration and ribavirin dose. Ann Intern Med 2004;140:346–355.

[57] Manns MP, Wedemeyer H, Cornberg M. Treating viral hepatitis C: efficacy, side effects, and complications. Gut 2006;55:1350–1359.

[58] Awad T, Thorlund K, Hauser G, Stimac D, Mabrouk M, Gluud C. Proceed with caution peginterferon alpha-2a versus peginterferon alfa-2b in chronic hepatitis C. A systematic review of randomized trials reply. Hepatology 2010;52:2241–2242.

[59] Manns M, Zeuzem S, Sood A, Lurie Y, Cornberg M, Klinker H, et al. Reduced dose and duration of peginterferon alfa-2b and weight-based ribavirin in patients with genotype 2 and 3 chronic hepatitis C. J Hepatol 2011.

[60] Sarrazin C, Susser S, Doehring A, Lange CM, Muller T, Schlecker C, et al. Importance of IL28B gene polymorphisms in hepatitis C virus genotype 2 and 3 infected patients. J Hepatol 2011;54:415–421.

[61] Poynard T, Colombo M, Bruix J, Schiff E, Terg R, Flamm S, et al. Peginterferon alfa-2b and ribavirin: effective in patients with hepatitis C who failed interferon alfa/ribavirin therapy. Gastroenterology 2009;136:1618–1628.

[62] Jensen DM, Marcellin P, Freilich B, Andreone P, Di Bisceglie A, Brandao-Mello CE, et al. Re-treatment of patients with chronic hepatitis C who do not respond to peginterferon-alpha 2b a randomized trial. Ann Intern Med 2009;150:W97–W528.

[63] Bedossa P. Liver biopsy. Gastroenterol Clin Biol 2008;32:4–7.

[64] Rousselet MC, Michalak S, Dupre F, Croue A, Bedossa P, Saint-Andre JP, et al. Sources of variability in histological scoring of chronic viral hepatitis. Hepatology 2005;41:257–264.

[65] Friedrich-Rust M, Ong MF, Martens S, Sarrazin C, Bojunga J, Zeuzem S, et al. Performance of transient elastography for the staging of liver fibrosis: a meta-analysis. Gastroenterology 2008;134:960–974.

[66] Castera L, Forns X, Alberti A. Non-invasive evaluation of liver fibrosis using transient elastography. J Hepatol 2008;48:835–847.

[67] Sebastiani G, Halfon P, Castera L, Pol S, Thomas DL, Mangia A, et al. SAFE biopsy: a validated method for large-scale staging of liver fibrosis in chronic hepatitis C. Hepatology 2009;49:1821–1827.

[68] Shaheen AA, Myers RP. Diagnostic accuracy of the APRI for the prediction of hepatitis C-related fibrosis: a systematic review. Hepatology 2007;46:833A.

[69] Degos F, Perez P, Roche B, Mahmoudi A, Asselineau J, Voitot H, et al. Diagnostic accuracy of FibroScan and comparison to liver fibrosis biomarkers in chronic viral hepatitis: a multicenter prospective study (the FIBROSTIC study). J Hepatol 2010;53:1013–1021.

[70] Parkes J, Guha IN, Roderick P, Harris S, Cross R, Manos MM, et al. Enhanced Liver Fibrosis (ELF) test accurately identifies liver fibrosis in patients with chronic hepatitis C. J Viral Hepat 2011;18:23–31.

[71] Parkes J, Roderick P, Harris S, Day C, Mutimer D, Collier J, et al. Enhanced Liver Fibrosis (ELF) Test can predict clinical outcomes in patients with chronic liver disease. Gut 2010;59:1245–1251.

[72] Castera L, Sebastiani G, Le Bail B, de Lédinghen V, Couzigou P, Alberti A. Prospective comparison of two algorithms combining non-invasive methods for staging liver fibrosis in chronic hepatitis C. J Hepatol 2010;52:191–198.

[73] Mangia A, Dalgard O, Minerva N, Verbaan H, Bacca D, Ring-Larsen H, et al. Ribavirin dosage in patients with HCV genotypes 2 and 3 who completed short therapy with peg-interferon alpha-2b and ribavirin. Aliment Pharmacol Ther 2010;31:1346–1353.

[74] Sarrazin C, Shiffman ML, Hadziyannis SJ, Lin A, Colucci G, Ishida H, et al. Definition of rapid virologic response with a highly sensitive real-time PCR-based HCV RNA assay in peginterferon alfa-2a plus ribavirin response-guided therapy. J Hepatol 2010;52:832–838.

[75] Wright M, Grieve R, Roberts J, Main J, Thomas HC. Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation. Health Technol Assess 2006;10:1–113.

[76] Grieve R, Roberts J, Wright M, Sweeting M, DeAngelis D, Rosenberg W, et al. Cost effectiveness of interferon or peginterferon with ribavirin for histologically mild chronic hepatitis C. Gut 2006;55:1332–1338.

[77] Sroczynski G, Esteban E, Conrads-Frank A, Schwarzer R, Muhlberger N, Wright D, et al. Long-term effectiveness and cost-effectiveness of antiviral treatment in hepatitis C. J Viral Hepat 2010;17:34–50.

[78] Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 2001;358:958–965.

[79] George SL, Bacon BR, Brunt EM, Mihindukulasuriya KL, Hoffmann J, Di Bisceglie AM. Clinical, virologic, histologic, and biochemical outcomes after successful HCV therapy: a 5-year follow-up of 150 patients. Hepatology 2009;49:729–738.
[80] Chevaliez S, Bouvier-Alias M, Brillet R, Pawlotsky JM. Overestimation and underestimation of hepatitis C virus RNA levels in a widely used real-time polymerase chain reaction-based method. Hepatology 2007;46:22–31.
[81] Diago M, Shiffman ML, Bronowicki JP, Zeuzem S, Rodriguez-Torres M, Pappas SC, et al. Identifying hepatitis C virus genotype 2/3 patients who can receive a 16-week abbreviated course of peginterferon alfa-2a (40 kDa) plus ribavirin. Hepatology 2010;51:1897–1903.
[82] Shiffman ML, Suter F, Bacon BR, Nelson D, Harley H, Sola R, et al. Peginterferon alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3. N Engl J Med 2007;357:124–134.
[83] Jensen DM, Morgan TR, Marcellin P, Pockros PJ, Reddy KR, Hadziyannis SJ, et al. Early identification of HCV genotype 1 patients responding to 24 weeks peginterferon alpha-2a (40 kD)/ribavirin therapy. Hepatology 2006;43:954–960.
[84] Ferenci P, Laferl H, Scherzer TM, Gschwantler M, Maieron A, Brunner H, et al. Peginterferon alfa-2a and ribavirin for 24 weeks in hepatitis C type 1 and 4 patients with rapid virological response. Gastroenterology 2008;135:451–458.
[85] Zeuzem S, Buti M, Ferenci P, Sperl J, Horsmans Y, Cianciara J, et al. Efficacy of 24 weeks treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C infected with genotype 1 and low pretreatment viremia. J Hepatol 2006;44:97–103.
[86] Fried MW. Side effects of therapy of hepatitis C and their management. Hepatology 2002;36:S237–S244.
[87] Soza A, Everhart JE, Ghany MG, Doo E, Heller T, Promrat K, et al. Neutropenia during combination therapy of interferon alfa and ribavirin for chronic hepatitis C. Hepatology 2002;36:1273–1279.
[88] Shiffman ML, Salvatore J, Hubbard S, Price A, Sterling RK, Stravitz RT, et al. Treatment of chronic hepatitis C virus genotype 1 with peginterferon, ribavirin, and epoetin alpha. Hepatology 2007;46:371–379.
[89] Afdhal NH, Dieterich DT, Pockros PJ, Schiff ER, Shiffman ML, Sulkowski MS, et al. Epoetin alfa maintains ribavirin dose in HCV-infected patients: a prospective, double-blind, randomized controlled study. Gastroenterology 2004;126:1302–1311.
[90] Pockros PJ, Shiffman ML, Schiff ER, Sulkowski MS, Younossi Z, Dieterich DT, et al. Epoetin alfa improves quality of life in anemic HCV-infected patients receiving combination therapy. Hepatology 2004;40:1450–1458.
[91] Berg T, Sarrazin C, Herrmann E, Hinrichsen H, Gerlach T, Zachoval R, et al. Prediction of treatment outcome in patients with chronic hepatitis C: significance of baseline parameters and viral dynamics during therapy. Hepatology 2003;37:600–609.
[92] Davis GL, Wong JB, McHutchison JG, Manns MP, Harvey J, Albrecht J. Early virologic response to treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C. Hepatology 2003;38:645–652.
[93] Mangia A, Minerva N, Bacca D, Cozzolongo R, Ricci GL, Carretta V, et al. Individualized treatment duration for hepatitis C genotype 1 patients: a randomized controlled trial. Hepatology 2008;47:43–50.
[94] Moreno C, Deltenre P, Pawlotsky JM, Henrion J, Adler M, Mathurin P. Shortened treatment duration in treatment-naive genotype 1 HCV patients with rapid virological response: a meta-analysis. J Hepatol 2010;52:25–31.
[95] Berg T, von Wagner M, Nasser S, Sarrazin C, Heintges T, Gerlach T, et al. Extended treatment duration for hepatitis C virus type 1: comparing 48 versus 72 weeks of peginterferon-alfa-2a plus ribavirin. Gastroenterology 2006;130:1086–1097.
[96] Pearlman BL, Ehleben C, Saifee S. Treatment extension to 72 weeks of peginterferon and ribavirin in hepatitis C genotype 1-infected slow responders. Hepatology 2007;46:1688–1694.
[97] Sanchez-Tapias JM, Diago M, Escartin P, Enriquez J, Romero-Gomez M, Barcena R, 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;131:451–460.
[98] Ferenci P, Laferl H, Scherzer TM, Maieron A, Hofer H, Stauber R, et al. Peginterferon alfa-2a/ribavirin for 48 or 72 weeks in hepatitis C genotypes 1 and 4 patients with slow virologic response. Gastroenterology 2010;138:503–512.
[99] Buti M, Lurie Y, Zakharova NG, Blokhina NP, Horban A, Teuber G, et al. Randomized trial of peginterferon alfa-2b and ribavirin for 48 or 72 weeks in patients with hepatitis C virus genotype 1 and slow virologic response. Hepatology 2010;52:1201–1207.
[100] Farnik H, Lange CM, Sarrazin C, Kronenberger B, Zeuzem S, Herrmann E. Meta-analysis shows extended therapy improves response of patients with chronic hepatitis C virus genotype 1 infection. Clin Gastroenterol Hepatol 2010;8:884–890.
[101] Dalgard O, Bjoro K, Ring-Larsen H, Bjornsson E, Holberg-Petersen M, Skovlund E, et al. Pegylated interferon alfa and ribavirin for 14 versus 24 weeks in patients with hepatitis C virus genotype 2 or 3 and rapid virological response. Hepatology 2008;47:35–42.
[102] Mangia A, Santoro R, Minerva N, Ricci GL, Carretta V, Persico M, et al. Peginterferon alfa-2b and ribavirin for 12 vs. 24 weeks in HCV genotype 2 or 3. New Engl J Med 2005;352:2609–2617.
[103] von Wagner M, Huber M, Berg T, Hinrichsen H, Rasenack J, Heintges T, et al. Peginterferon-alpha-2a (40 kDa) and ribavirin for 16 or 24 weeks in patients with genotype 2 or 3 chronic hepatitis C. Gastroenterology 2005;129:522–527.
[104] Yu ML, Dai CY, Huang JF, Hou NJ, Lee LP, Hsieh MY, et al. A randomised study of peginterferon and ribavirin for 16 versus 24 weeks in patients with genotype 2 chronic hepatitis C. Gut 2007;56:553–559.
[105] Kau A, Vermehren J, Sarrazin C. Treatment predictors of a sustained virologic response in hepatitis B and C. J Hepatol 2008;49:634–651.
[106] Romero-Gomez M, Fernandez-Rodriguez CM, Andrade RJ, Diago M, Alonso S, Planas R, et al. Effect of sustained virological response to treatment on the incidence of abnormal glucose values in chronic hepatitis C. J Hepatol 2008;48:721–727.
[107] Zeuzem S, Hultcrantz R, Bourliere M, Goeser T, Marcellin P, Sanchez-Tapias J, et al. Peginterferon alfa-2b plus ribavirin for treatment of chronic hepatitis C in previously untreated patients infected with HCV genotypes 2 or 3. J Hepatol 2004;40:993–999.
[108] Lam KD, Trinh HN, Do ST, Nguyen TT, Garcia RT, Nguyen T, et al. Randomized controlled trial of pegylated interferon-alfa 2a and ribavirin in treatment-naive chronic hepatitis C genotype 6. Hepatology 2010;52:1573–1580.
[109] Zhou YQ, Wang XH, Hong GH, Zhu Y, Zhang XQ, Hu YJ, et al. Twenty-four weeks of pegylated interferon plus ribavirin effectively treat patients with HCV genotype 6a. J Viral Hepat 2010. doi:10.1111/j.1365-2893.2010.01373.
[110] McHutchison JG, Manns M, Patel K, Poynard T, Lindsay KL, Trepo C, et al. Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C. Gastroenterology 2002;123:1061–1069.
[111] Mauss S, Berger F, Goelz J, Jacob B, Schmutz G. A prospective controlled study of interferon-based therapy of chronic hepatitis C in patients on methadone maintenance. Hepatology 2004;40:120–124.
[112] Schaefer M, Hinzpeter A, Mohmand A, Janssen G, Pich M, Schwaiger M, et al. Hepatitis C treatment in "difficult-to-treat" psychiatric patients with pegylated interferon-alpha and ribavirin: response and psychiatric side effects. Hepatology 2007;46:991–998.
[113] Schaefer M, Schmidt F, Folwaczny C, Lorenz R, Martin G, Schindlbeck N, et al. Adherence and mental side effects during hepatitis C treatment with interferon alfa and ribavirin in psychiatric risk groups. Hepatology 2003;37:443–451.
[114] Bressler BL, Guindi M, Tomlinson G, Heathcote J. High body mass index is an independent risk factor for nonresponse to antiviral treatment in chronic hepatitis C. Hepatology 2003;38:639–644.
[115] Anand BS, Currie S, Dieperink E, Bin EJ, Shen H, Ho SB, et al. Alcohol use and treatment of hepatitis C virus: results of a national multicenter study. Gastroenterology 2006;130:1607–1616.
[116] Romero-Gomez M, Viloria MD, Andrade RJ, Salmeron J, Diago M, Fernandez-Rodriguez CM, et al. Insulin resistance impairs sustained response rate to peginterferon plus ribavirin in chronic hepatitis C patients. Gastroenterology 2005;128:636–641.
[117] Thevenot T, Cadranel JF, Di Martino V, Pariente A, Causse X, Renou C, et al. A national French survey on the use of growth factors as adjuvant treatment of chronic hepatitis C. Hepatology 2007;45:377–383.
[118] McHutchison JG, Dusheiko G, Shiffman ML, Rodriguez-Torres M, Sigal S, Bourliere M, et al. Eltrombopag for thrombocytopenia in patients with cirrhosis associated with hepatitis C. New Engl J Med 2007;357:2227–2236.
[119] Afdhal N, Giannini E, Tayyab GN, Mohsin A, Lee JW, Andriulli A, et al. Eltrombopag in chronic liver disease patients with thrombocytopenia undergoing an elective invasive procedure: results from elevate, a randomised clinical trial. J Hepatol 2010;52:S460.
[120] Bezemer G, Van Gool AR, Drenth JP, Hansen BE, Fortuyn HAD, Weegink CJ, et al. A double blind, placebo-controlled trial with escitalopram to prevent psychiatric adverse events during treatment with pegylated interferon-alpha and ribavirin for chronic hepatitis c: the "prevention of psychiatric side effects (Pops)-study". Hepatology 2008;48:1139A.

Clinical Practice Guidelines

[121] Schaefer M, Mauss S. Hepatitis C treatment in patients with drug addiction: clinical management of interferon-alpha-associated psychiatric side effects. Curr Drug Abuse Rev 2008;1:177–187.

[122] Zeuzem S, Berg T, Moeller B, Hinrichsen H, Mauss S, Wedemeyer H, et al. Expert opinion on the treatment of patients with chronic hepatitis C. J Viral Hepat 2009;16:75–90.

[123] Di Bisceglie AM, Shiffman ML, Everson GT, Lindsay KL, Everhart JE, Wright EC, et al. Prolonged therapy of advanced chronic hepatitis C with low-dose peginterferon. N Engl J Med 2008;359:2429–2441.

[124] Lok AS, Everhart JE, Wright EC, Di Bisceglie AM, Kim HY, Sterling RK, et al. Maintenance peginterferon therapy and other factors associated with hepatocellular carcinoma in patients with advanced hepatitis C. Gastroenterology 2010.

[125] Schmid M, Kreil A, Jessner W, Homoncik M, Datz C, Gangl A, et al. Suppression of haematopoiesis during therapy of chronic hepatitis C with different interferon alpha mono and combination therapy regimens. Gut 2005;54:1014–1020.

[126] Garcia-Retortillo M, Forns X, Feliu A, Moitinho E, Costa J, Navasa M, et al. Hepatitis C virus kinetics during and immediately after liver transplantation. Hepatology 2002;35:680–687.

[127] Forns X, Garcia-Retortillo M, Serrano T, Feliu A, Suarez F, de la Mata M, et al. Antiviral therapy of patients with decompensated cirrhosis to prevent recurrence of hepatitis C after liver transplantation. J Hepatol 2003;39:389–396.

[128] Everson G, Trouillot T, Trotter J, Halprin A, McKinley C, Fey B. Treatment of decompensated cirrhotics with a low accelerating dose regimen (LADR) of interferon-alfa-2b plus ribavirin: safety and efficacy. Hepatology 2001;32:595.

[129] Carrion JA, Martinez-Bauer E, Crespo G, Ramirez S, Perez-del-Pulgar S, Garcia-Valdecasas JC, et al. Antiviral therapy increases the risk of bacterial infections in HCV-infected cirrhotic patients awaiting liver transplantation: a retrospective study. J Hepatol 2009;50:719–728.

[130] Prieto M, Berenguer M, Rayon JM, Cordoba J, Arguello L, Carrasco D, et al. High incidence of allograft cirrhosis in hepatitis C virus genotype 1b infection following transplantation: relationship with rejection episodes. Hepatology 1999;29:250–256.

[131] Forman LM, Lewis JD, Berlin JA, Feldman HI, Lucey MR. The association between hepatitis C infection and survival after orthotopic liver transplantation. Gastroenterology 2002;122:889–896.

[132] Berenguer M, Palau A, Aguilera V, Rayon JM, Juan FS, Prieto M. Clinical benefits of antiviral therapy in patients with recurrent hepatitis C following liver transplantation. Am J Transplant 2008;8:679–687.

[133] Neumann UP, Berg T, Bahra M, Seehofer D, Langrehr JM, Neuhaus R, et al. Fibrosis progression after liver transplantation in patients with recurrent hepatitis C. J Hepatol 2004;41:830–836.

[134] Blasco A, Forns X, Carrion JA, Garcia-Pagan JC, Gilbert R, Rimola A, et al. Hepatic venous pressure gradient identifies patients at risk of severe hepatitis C recurrence after liver transplantation. Hepatology 2006;43:492–499.

[135] Samuel D, Bizollon T, Feray C, Roche B, Ahmed SNS, Lemonnier C, et al. Interferon-alpha 2b plus ribavirin in patients with chronic hepatitis C after liver transplantation: a randomized study. Gastroenterology 2003;124:642–650.

[136] Carrion JA, Navasa M, Garcia-Retortillo M, Garcia-Pagan JC, Crespo G, Bruguera M, et al. Efficacy of antiviral therapy on hepatitis C recurrence after liver transplantation: a randomized controlled study. Gastroenterology 2007;132:1746–1756.

[137] Qurishi N, Kreuzberg C, Luchters G, Effenberger W, Kupfer B, Sauerbruch T, et al. Effect of antiretroviral therapy on liver-related mortality in patients with HIV and hepatitis C virus coinfection. Lancet 2003;362:1708–1713.

[138] Sulkowski MS. Viral hepatitis and HIV coinfection. J Hepatol 2008;48:353–367.

[139] Alberti A, Clumeck N, Collins S, Gerlich W, Lundgren J, Palu G, et al. Short statement of the first European consensus conference on the treatment of chronic hepatitis B and C in HIV co-infected patients. J Hepatol 2005;42:615–624.

[140] Potthoff A, Manns MP, Wedemeyer H. Treatment of HBV/HCV coinfection. Expert Opin Pharmacother 2010;11:919–928.

[141] Potthoff A, Wedemeyer H, Boecher WO, Berg T, Zeuzem S, Arnold J, et al. The HEP-NET B/C co-infection trial: a prospective multicenter study to investigate the efficacy of pegylated interferon-alpha 2b and ribavirin in patients with HBV/HCV co-infection. J Hepatol 2008;49:688–694.

[142] Potthoff A, Berg T, Wedemeyer H. Late hepatitis B virus relapse in patients co-infected with hepatitis B virus and hepatitis C virus after antiviral treatment with pegylated interferon-a2b and ribavirin. Scand J Gastroenterol 2009;44:1487–1490.

[143] Peck-Radosavljevic M, Boletis J, Besisik F, Ferraz ML, Alric L, Samuel D, et al. Low-dose peginterferon alfa-2a (40KD) is safe and produces a SVR in patients with chronic hepatitis C and end-stage renal disease. Clin Gastroenterol Hepatol 2011;9:242–248.

[144] Potthoff A, Wiegand J, Luth JB, Wedemeyer H, Manns MP, Tillmann HL. Superiority of standard interferon-alpha2b compared to pegylated interferon-alpha2b (12 kDa) in a hemodialysis patient with chronic hepatitis C? Clin Nephrol 2005;63:232–235.

[145] Fabrizi F, Dixit V, Martin P, Messa P. Combined antiviral therapy of hepatitis C virus in dialysis patients: meta-analysis of clinical trials. J Viral Hepat 2010. doi:10.1111/j.1365-2893.2010.01405.x.

[146] Gane E, Pilmore H. Management of chronic viral hepatitis before and after renal transplantation. Transplantation 2002;74:427–437.

[147] Martin P, Fabrizi F. Hepatitis C virus and kidney disease. J Hepatol 2008;49:613–624.

[148] Orens JB, Estenne M, Arcasoy S, Conte JV, Corris P, Egan JJ, et al. International guidelines for the selection of lung transplant candidates: 2006 update – a consensus report from the pulmonary scientific council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2006;25:745–755.

[149] Safdar K, Schiff ER. Alcohol and hepatitis C. Semin Liver Dis 2004;24:305–315.

[150] Edlin BR. Prevention and treatment of hepatitis C in injection drug users. Hepatology 2002;36:S210–S219.

[151] Harmatz P, Jonas MM, Kwiatkowski JL, Wright EC, Fischer R, Vichinsky E, et al. Safety and efficacy of pegylated interferon alpha-2a and ribavirin for the treatment of hepatitis C in patients with thalassemia. Haematol – Hematol J 2008;93:1247–1251.

[152] Strader DB, Wright T, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C. Hepatology 2004;39:1147–1171.

[153] Wiegand J, Jackel E, Cornberg M, Hinrichsen H, Dietrich M, Kroeger J, et al. Long-term follow-up after successful interferon therapy of acute hepatitis C. Hepatology 2004;40:98–107.

[154] Wiegand J, Buggisch P, Boecher W, Zeuzem S, Gelbmann CM, Berg T, et al. Early monotherapy with pegylated interferon alpha-2b for acute hepatitis C infection: the HEP-NET acute-HCV-II study. Hepatology 2006;43:250–256.

[155] Mondelli MU, Cerino A, Cividini A. Acute hepatitis C: diagnosis and management. J Hepatol 2005;42:S108–S114.

[156] Dienstag JL. Management of hepatitis C – reply. Gastroenterology 2006;131:332–333.

[157] Hofer H, Watkins-Riedel T, Janata O, Penner E, Gangl A, Ferenci P. Spontaneous viral clearance in patients with acute hepatitis C: predictability by repeated measurements of serum HCV concentration. Hepatology 2002;36:286A.

[158] Flisiak R, Parfieniuk A. Investigational drugs for hepatitis C. Expert Opin Invest Drugs 2010;19:63–75.

[159] Zeuzem S, Andreone P, Pol S, Lawitz EJ, Diago M, Roberts S, Focaccia R, Younossi ZM, Foster GR, Horban A, Pockros PJ, Van Heeswijk R, de Meyer S, Luo D, Picchio G, Beumont M. Realize trial final results: telaprevir-based regimen for genotype 1 hepatitis C virus infection in patients with prior null response, partial response or relapse to peginterferon/ribavarin. Abstracts of the International Liver Congress™ 2011.