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Latin American Association for the Study of the Liver Practice Guidelines

Diagnosis, management, and treatment of hepatitis C

This document has been approved by the Latin American Association for the Study of the Liver (ALEH)

PREAMBLE

The following recommendations provide an approach to the establishment of guidelines for the diagnosis, management, and treatment of hepatitis C virus infection. These guidelines are based on a formal analysis and review of recently published literature around the world.

Written for use especially by physicians, the recommendations suggest a range of possibilities for the epidemiology, diagnosis, and Treatment of Hepatitis C infection, but without any intention of establishing standards of care for individual patients. Although we suggest that the recommendations in these guidelines be applied appropriately according to the history of each patient, we emphasize the flexible character (individualization) of these recommendations because they are written as guidelines.

INTRODUCTION

Approximately 20 years ago, Houghton, *et al.*, discovered hepatitis C virus (HCV), which was established as the main cause of non-A non-B hepatitis. Since then, important advances have been made in the knowledge of the disease's biological characteristics and diagnosis and also of its natural history and treatment.[1,2] The first consensus conference on hepatitis C was organized in the United States in 1997 and several meetings have since been conducted in order to present and discuss the most important advances in the evolution and management of the infection.

The burden of hepatitis C is of enormous interest because of the natural course of this illness, which can lead to cirrhosis and hepatocellular carcinoma (HCC) after an asymptomatic period that may last for 25 to 30 years. It is important to know the characteristics of the infection: current findings about the progression of the disease suggest that almost 80% of patients convert to a chronic disease, at a high human and economic cost. Recent trend studies predict that HCV-related mortality will continue to increase over coming decades.[3-5]

The main objectives of these guidelines are to make recommendations on diagnosis, to propose preventive actions against infection, and to set up general guidelines on treatment in different risk groups. To establish the quality of evidence that supports the recommendations in these guidelines, a class and level of evidence have been assigned to each recommendation, the former reflecting benefit *vs.* risk and the latter the strength of the recommendation (Table 1).[6]

EPIDEMIOLOGY

Several studies have estimated that approximately 180 million people around the world are infected with HCV. In Latin America, the prevalence in the general population is around 1.3%, one of the lowest in the world.[7] Nevertheless, the prevalence varies

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Table 1.

Classification	Description
Class I	Conditions for which there is evidence or general consensus that the particular diagnostic procedure or treatment is beneficial, useful, and effective.
Class II	Conditions for which there is conflicting evidence and/or divergence in opinions about the utility and efficacy of a diagnostic evaluation, procedure, or treatment.
Class IIa	The weight of evidence/opinion is in favor of utility and efficacy.
Class IIb	The utility and/or efficacy are less well established by evidence or opinion.
Class III	Conditions in which there is evidence or general consensus that a diagnostic evaluation, procedure, or treatment is not useful or effective and in some cases may cause damage.
Evidence level	**Description**
Level A	Data derived from multiple randomized studies or meta-analysis.
Level B	Data derived from only one randomized study or nonrandomized studies.
Level C	Experts' opinions, case studies, or treatment standards.

Adapted from: Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management and treatment of hepatitis C: an update. *Hepatology* 2009; 49(4): 1335–74.

Table 2. Prevalence of HCV in different risk groups.

Country	General population	Blood donors	IVDU	Hemodialysis	Coinfection with HBV
Mexico	1.4%	1.4%	4%	6.7%[2]	
Dominican Republic	1.5%		2.4%[4]	49%	
Puerto Rico	2.4%				
Costa Rica	0.3–2%	0.2-0.3%	0%[1]		
Venezuela			4%	71%[3]	
Brazil	1.32%				
Peru	1.2%	1.1%	2%	51%	
Chile	1.2%	1.2%			
Argentina	2.1%	0.79%	62%	19%	30%

[1]Patiño J, Hevia F, Saenz R, Nuñez P, Rodríguez R, Horwitz D, Flores J. Trabajo 69 XIII Jornadas Latinoamericanas de Hepatologia. *Rev Gastroenterol Mex* 1994; 59(suppl. 2). [2]Méndez-Sánchez N, Motola-Kuba D, Chávez-Tapia NC, et al. Prevalence of hepatitis C virus infection among hemodialysis patients at a tertiary-care hospital in Mexico City, Mexico. *J Clin Microbiol* 2004; 42: 4321–2. [3]Pujol FH, Ponce JG, Lema MG, et al. High incidence of hepatitis C virus infection in hemodialysis patients in units with high prevalence. *J Clin Microbiol* 1996; 34: 1633–6. [4]Hogar Crea Dominicano. Propuesta para proyecto. Proyecto de capacitación y sensibilización en relación a las ITS el VIH y el SIDA con ex-usuarios de drogas (UD) comunidades residenciales de Hogar Crea Dominicano., Inc.

between countries and between regions in each country. Regional studies on this topic have estimated prevalence in the general population, and some countries have data regarding various risk groups (Table 2).

In Mexico, a prevalence lower than 2% has been estimated; Chiquete et al, reported a prevalence between 0.5% and 2%,[8] and Valdespino et al, found a general prevalence of 1.6%.[9] In Brazil, several studies carried out in the general population in different regions of that country have estimated a mean prevalence of 1.32% of HCV.[10] General population studies have not been carried out in the Dominican Republic, but data from the Public Health Department estimate a prevalence of 1.5%.[11] In Puerto Rico, studies carried out in the general population have estimated a prevalence of 2.4%; Perez, *et al.*, determined that the seroprevalence is similar to that found in the US general population, but concluded that further research is needed in that region.[12]

In the Dominican Republic, several studies in risk groups determined a prevalence of 2% in men who have sex with men and a study carried out in the sugarcane fields of the province of Barahona determined a prevalence of 5.3% in this group of working women.[13] In Costa Rica, studies carried out among voluntary blood donors between 1992 and 2008 esti-

mated a prevalence of 0.3% to 2%,[14-16] and in Peru, the prevalence among blood donors has been reported to be 0.8% to 1.2%.[17] In Chile, studies carried out in blood donors have estimated a prevalence of around 0.3%. However, the National Health Survey showed a prevalence of 0.12% and studies carried out in Santiago revealed a prevalence of 1.15%.[18]

Although no large-scale population studies have been carried out in Argentina, several studies according to the National Consensus on hepatitis C estimate a prevalence of about 2.1%.[19]

Recommendations

1. *Large-scale population studies must be carried out in every Latin American countries to gather better and complete data about the prevalence of hepatitis C in the region* ***(Class I, Level C).***

TRANSMISSION ROUTES

To assist in creating new methods of control and therapy, it is mandatory to identify the different means of transmission of HCV. HCV can be transmitted by several parenteral routes, of which blood transfusion and intravenous drug use (IVD) are the most common. In developed countries, the main transmission route is the use of intravenous drugs, but in Latin America, several studies show that the main transmission route continues to be transfusion of blood and its derivatives. The frequency of infection by this route has diminished because of the establishment in around 1992 of screening measures in blood banks. However, although current methods for the selection of blood donors and the screening tests are highly developed and the risk of transmission is far lower than 15 years ago, the risk remains. At the same time, intravenous and intranasal drug abuse is increasing in Latin America, making it the second most important route of transmission. According to the current epidemiological model, it is possible that in a few years it will be the main form of transmission, similar to the United States and Europe.[6,20] The use of contaminated needles and paraphernalia is one of the most effective modes of transmission of HCV. Several studies have shown that 65% of infected intravenous drugs users (IVDU) acquire the virus during the first year of drug abuse.[21]

Other potential means of transmission include contact with one or more infected sexual partners, although the prevalence is higher in persons with several partners than in monogamous couples. Even though it is practical to advise HCV carriers that they should inform their partners of their condition, they should be equally informed that the risk of catching the disease is low, as only 1% to 5% of monogamous couples become HCV positive when one of the partners is a carrier. However, the transmission rate increases in persons with multiple sexual partners and persons who have sexual intercourse with prostitutes, anal intercourse, traumatic relations, or intercourse during menses or with inadequate lubrication. Despite the low risk, the use of prophylactic condoms is recommended to nonmonogamous couples. No limitations are recommended on the daily activities of persons with HCV except in the use of razor blades and tooth brushes that should not be shared with other people.

By contrast, vertical transmission occurs in approximately 5% of the children born from an infected mother, with the risk further increased if the mother is also infected with human immunodeficiency virus (HIV). Nevertheless, there is currently not enough information to recommend a managed form of delivery.[22-24]

Hemodialysis patients have an increased risk of acquiring the infection. The prevalence in hemodialysis patients in Latin America is reported as ranging from 6.7% in Mexico to 71% in Venezuela.[25,26] For healthcare workers, the main risk is through accidental contact with contaminated needles and percutaneous injuries, with the risk of infection being 1.8%; a lower prevalence occurs through contact with exposed mucosa.[27] Other less common forms of transmission are tattooing and body piercing; because of this, screening is recommended in this high-risk population and in IVDU.

Recommendations

1. *Blood donors who have a positive result during screening should be informed in order to prevent transmission* ***(Class I, Level C).***
2. *Persons infected with HCV should be counseled with the intention of avoiding transmission to others* ***(Class I, Level C).***
3. *Persons infected with HCV should be counseled with the intention of avoiding donation of blood, organs, other tissues, and semen* ***(Class I, Level C).***
4. *Viral Hepatitis screening should be mandatory in every blood donor.* ***(Class I, Level A).***

DIAGNOSIS

Because patients with chronic infection generally are asymptomatic, to date the best way to diagnose the infection is screening persons with risk factors and a history of exposure to the virus, in addition to counseling.

Diagnostic tests are classified into serological tests, which identify specific anti-HCV IgG, and molecular tests that identify viral nucleic acid. The initial evaluation is through third-generation immunoenzymatic techniques that identify antibodies against different epitopes of HCV and that have sensitivity and specificity of 97% and 99%, respectively. Also available is the recombinant immunoblot assay (RIBA), which was originally developed as a more specific test to confirm results from ELISA. However, this is about to fall into disuse because of the usefulness of ELISA. Although HCV antibodies remain detectable lifelong in immunocompetent patients with chronic infection, in patients that recover spontaneously, antibodies tend to disappear within 18 to 20 years. Thus, detection of antibodies indicates contact with the virus only and does not discriminate between acute, chronic, or resolved infection. Interestingly, confirmation of an active HCV infection is performed by demonstrating the presence of HCV-RNA through quantitative detection by RNA amplification methods such as polymerase chain reaction (PCR) or transcription mediated amplification (TMA).[6] These assays must have a sensitivity of at least 50 IU/mL. Viral RNA can be detected 2 weeks post infection while antibodies are detectable 8 to 12 weeks after contact; therefore, adequate interpretation is required within the different contexts of the test results.

Because of the great genomic variability of HCV, of which six types and more than 90 subtypes are known, genotype determination is useful in epidemiological studies and to identify and predict the possibility of resistance to treatment and the appropriate duration for patient treatment and follow-up.

Recommendations

1. *Screening in the general population is not recommended* ***(Class I, Level C).***
2. *Determination of anti-HCV antibodies is the test of choice for the initial diagnosis in patients with suspected acute or chronic HCV infection* ***(Class I, Level A).***
3. *Anti-HCV determination should be done in patients with the following risk factors* ***(Class IIa, Level B):***

   a) *People who received a blood transfusion before 1992.*
   b) *Intravenous drug users.*
   c) *Patients in hemodialysis.*
   d) *Patients with elevated aminotransferases.*
   e) *Healthcare workers exposed to infected blood.*
   f) *Patients with hemophilia who received clotting factor concentrates before 1987.*
   g) *Children born to mothers infected with HCV.*
   h) *Sexual partners of hepatitis C patients.*
   i) *HIV infected patients.*

4. *Viral RNA analysis should be done in:*

   a) *Patients positive for anti-HCV antibodies* ***(Class I, Level B).***
   b) *Patients in whom antiviral treatment is considered* ***(Class I, Level A).***
   c) *Immunosuppressed patients with unexplained chronic elevation of aminotransferase levels.* ***(Class I, Level B).***

UTILITY OF LIVER BIOPSY IN CHRONIC INFECTION

Liver biopsy is a procedure indicated in a broad spectrum of diseases. The basic requirements for its use are the benefits that it will bring to the patient, as well as the impossibility of obtaining the same detailed information with any other procedure. Possible benefits include identification of liver status, identification of useful characteristics at the time of treatment decisions, or monitoring of the advance of fibrosis or cirrhosis that needs surveillance for HCC. However, the use of this diagnostic procedure in chronic HCV has been questioned in recent years. In addition, the act of soliciting a biopsy can be a challenge because of its invasiveness and because patients correlate the procedure with malignancy. However, advances in surgical techniques and the control of hemorrhage in the second half of last century have diminished complications during this procedure. Liver biopsy continues to be the preferred method to allow evaluation of the grade and stage of hepatic lesions. Patients with confirmed serology for Hepatitis C and clinical and/or laboratorial data for other associated diseases, as auto-immune or metabolic disorders, certainly deserve liver biopsy for differential diagnosis

Table 3. Fibrosis evaluation scales.

Stage	IASL[1]	Metavir[2]
0	Non fibrosis	Non fibrosis
1	Mild fibrosis	Periportal fibrotic expansion
2	Moderate fibrosis	Periportal septa
3	Severe fibrosis	Portocentral septa
4	Cirrhosis	Cirrhosis

[1]Desmet VJ, Gerber M, Hoofnagle JH, Manns M, Scheuer PJ. Classification of chronic hepatitis: diagnosis, grading and staging. *Hepatology* 1994; 19: 1513–20. [2]Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR cooperative study group. *Hepatology* 1996; 24: 289–93.

Although liver biopsy has been established as the "gold standard" in the diagnosis of chronic hepatitis C, it is not without contraindications and complications. The main contraindications to biopsy are alterations in coagulation and tense ascites. A prolonged prothrombin time and a low platelet count are major risk factors for bleeding. In addition, because of the possible subjectivity of histological description and interpretation, numeric systems have been proposed to make classification of necrosis, inflammation, and fibrosis less subjective (Table 3).

Recommendations

1. *Liver biopsy is essential in those patients with hepatitis C in whom more information is required about the stage of fibrosis and/or grade of peri-portal or lobular inflammation, for prognostic purposes* ***(Class I, Level A).***
2. *For patients with presumed associated conditions, as auto-immune or metabolic disorders, a liver biopsy can effectively make a differential diagnosis* ***(Class I, Level B).***

USE OF NONINVASIVE METHODS TO EVALUATE THE STAGE OF LIVER FIBROSIS

Although liver biopsy is considered the "gold standard" for the diagnosis of hepatic fibrosis, because of its complications and technical difficulty, noninvasive methods have been developed for the evaluation of fibrosis. However, such methods are most effective for the early stages of disease with little fibrosis or cirrhosis, leaving the intermediate stages without a reliable diagnostic method. One of the new methods is transient elastography; this method has not fulfilled all the criteria necessary to replace hepatic biopsy but has proven its efficacy in the diagnosis of fibrosis extension when combined with other noninvasive methods.

Recently, noninvasive methods such as transient elastography and FibroTest ® have been studied in patients with persistently normal alanine transaminase (ALT) levels. The results show that transient elastography might be very useful in the selection of patients with significant fibrosis for antiviral therapy, and eventually remove the need for taking a liver biopsy.

INDICATIONS AND CONTRAINDICATIONS FOR THE TREATMENT OF HCV INFECTION

Evidence shows that 55% to 85% of HCV-infected patients will remain infected through their lifetime. The risk of developing cirrhosis rises from 5% to 25% over a period of 30 years.[28] Prior to treatment, it is necessary to know the stage of liver disease, to determine the presence of compensated or decompensated cirrhosis or portal hypertension, and to know factors such as age, comorbidities, extrahepatic manifestations such as cryoglobulinemia and glomerulonephritis, and quality of life.

Consensus indicates that treatment should be with a combination of pegylated interferon and ribavirin. Medical treatment is indicated in patients who are anti-HCV positive and HCV-RNA positive and in whom histological evidence indicates chronic hepatitis.

The goal of treatment is to prevent complications and death related to HCV infection. Because of the chronic evolution of the disease, the response is determined by several biochemical, virological, or his-

Table 4. Characteristics of patients for whom therapy is recommended.

- Age 18 to 70 years.
- HCV antibody positive in serum.
- Positive for HCV RNA.
- Hepatic biopsy: chronic hepatitis with significant fibrosis.
- Compensated liver disease.
  - Absence of gastroesophagic varicose veins.
  - Total bilirubin < 1.5 g/dL.
  - International normalized ratio (INR) < 1.5.
  - Albumin > 3.4 g/100mL.
  - Platelet count of 75,000/mm^3.
  - No evidence of hepatic decompensation (hepatic encephalopathy or ascites).
- Hemoglobin ≥ 13 g/dL for men and 12 g/dL for women.
- Neutrophil count ≥ 1500/mm^3.
- Creatinine < 1.5 mg/dL.
- Willingness to be treated.
- No contraindications.

Table 5. Contraindications for HCV treatment.

- Major uncontrolled depressive disorder and other mental disturbances.
- Posttransplantation patients.
- Autoimmune diseases that might be exacerbated by treatment with pegylated interferon.
- Untreated thyroid disease.
- Pregnancy.
- Severe comorbidity such as arterial hypertension, heart failure, uncontrolled diabetes mellitus, chronic obstructive pulmonary disease, or epilepsy.
- Age under 2 years.
- Known hypersensitivity to treatment.

tological variables including normalization of ALT levels, absence of viral RNA on PCR, or improvement of at least two points on the scale of necroinflammation or fibrosis scores.

Current recommendations to treat chronic HCV-infected patients have been suggested from randomized clinical trials. Characteristics of patients in whom therapy is accepted are shown in Table 4, and characteristics of patients in whom therapy is contraindicated are shown in Table 5.

Patients with HCV genotype 2 or 3 may be treated in any stage of the disease because of the elevated frequency of sustained virological response (SVR) in those groups.

Recommendations

1. *The decision to establish therapy for any patient has to be individualized, with awareness of the severity of liver damage, the probability of response to treatment, the potential for severe adverse effects, and the presence of comorbidities* ***(Class I, Level A).***
2. *The ideal patients to treat are those with chronic hepatitis C, with genotype 2 and 3 and low viral load and those who have Child A liver cirrhosis associated with > 75,000 platelets/ml and hemoglobin > 12 g/dL* ***(Class I, Level A).***
3. *Combined treatment with pegylated interferon and ribavirin is contraindicated in patients with:*

   a) Decompensated psychiatric disease.
   b) Decompensated diabetes mellitus.
   c) Decompensated arterial hypertension.
   d) Decompensated hemoglobinopathy.
   e) Autoimmune disease with the exception of treated autoimmune thyroid disease.
   f) Immunosuppressive treatment.
   g) Thrombocytopenia < 50,000 platelets/mL.
   h) Neutropenia < 750 cells/mL.
   i) Hemoglobin < 12g/dL.

   (Class II, Level A).

PREDICTIVE FACTORS FOR THE RESPONSE TO TREATMENT

During treatment, several types of virological response may occur, the most important of which is the SVR, which is defined as the absence of detectable serum viral RNA by PCR assay for 24 weeks after suspension of treatment. Knowledge prior to treatment of the factors predictive of treatment response is useful to predict SVR. The combination of pegylated interferon with ribavirin has an SVR in 50% to 80% of patients. However, this rate is still low considering the adverse effects, costs, and duration of treatment.

It is possible to predict SVR before the beginning of treatment if several characteristics of the virus or of the host are known, such as viral genotype (1 *vs.* non-1), pretreatment viral load, fibrosis stage, gamma-glutamyl transpeptidase (GGTP), age, race, weight, and insulin resistance. Other predictive factors might be identified after initiating treatment, such as the rapid viral response (RVR; viral RNA not detectable by the fourth week of treatment) and the early viral response (EVR; a reduction of at least 2 log in viral load by the 12th week or a negative HCV-PCR).[29-32] In patients with HCV genotype 1, the rate of response to treatment based on pegylated interferon and ribavirin is 40%, whereas in patients with genotype 2 or 3 it is around 80%.

Another important factor is coinfection with other viruses, because a lower rate of response to treatment has been observed in patients coinfected with hepatitis B virus (HBV). In HIV-coinfected patients, development of fibrosis is faster and the progression to liver failure and hepatocellular carcinoma occurs earlier, but response rates are similar to those of patients without HIV coinfection.

Patients with hepatitis C and cirrhosis have lower rates of sustained response. Even when cirrhosis is absent, the probability of response to treatment diminishes as the stage of fibrosis increases. In addition, treatment compliance has been demonstrated to be a fundamental factor in treatment effectiveness, so that every effort must be made to ensure the patient maintains the dose and duration of treatment.[33]

However, and despite the inadequate predictive factors for response, it is possible that in the near

future, new techniques will be developed. These could include the identification of individual genetic polymorphisms such as the one found near the IL-28B gene encoding interferon γ3 that is associated with an approximately twofold change in response to treatment[34] and profiles of protein expression that will open up a new world of possibilities to better identify good and bad responders to HCV therapy. It is considered that complete remission of the infection has occurred when there is no detectable viral load of HCV 6 months after the completion of a course of treatment.

Recommendations

1. *The major pre-treatment predictive factors for treatment response are viral load, viral genotype, and fibrosis stage. Recently RVR has been appointed as the most important predictive factor of SVR.* ***(Class I, Level A).***
2. *The principal negative predictive factor is a detectable viral load or a reduction of less than 2 logs by the 12th week of treatment* ***(Class I, Level A).***

HEPATITIS C TREATMENT IN NAÏVE PATIENTS

The selection of candidate patients to receive treatment should take into consideration several factors including: the probability of response, the likelihood for adverse effects, cost, and effectiveness of treatment.

The aim of therapy is to prevent long-term complications and death caused by this disease. In the short term, SVR, normalization of ALT levels (if abnormal), and histological improvement are more important. This is achieved with viral eradication, which is defined as undetectable viral RNA 6 months after finishing therapy (SVR). All HCV-infected people are potentially treatable unless contraindications exist.

The therapeutic regimens depend on the type of interferon and the viral genotype. It has been confirmed by several studies that treatment should include a combination of pegylated interferon plus ribavirin because of its greater efficacy compared with monotherapy of interferon and with the combination of standard interferon plus ribavirin. A meta-analysis recently published comparing both types of pegylated interferons showed a trend toward higher SVR rates with peginterferon alpha 2a (47%) compared with peginterferon alpha 2b (41%).[35] Treatment must also be strictly supervised by experts in order to document its effectiveness and safety.

Table 6. Ribavirin dose by weight.

Weight (kg)	Ribavirin dose (mg)
< 65	800
65–85	1,000
85–105	1,200
> 105	1,400

Modified from: Jen J, Laughlin M, Chung C, et al. Ribavirin dosing in chronic hepatitis C: application of population pharmacokinetic-pharmacodynamic models. *Clin Pharmacol Ther* 2002; 72(4): 349–61.

Patients with HCV genotype 1 are considered difficult to cure because the SVR rate is considerably lower in this group of patients than in patients with non-1 genotype HCV. For this reason, several studies have been carried out that demonstrate that treatment with pegylated interferon and ribavirin at higher doses for a period of 48 weeks may obtain a greater rate of SVR.[30,31]

For patients with HCV genotype 2 or 3, it has been established that treatment should be for 24 weeks with a combination of pegylated interferon plus ribavirin, which shows an effectiveness around 80%-90%.[36] However, patients with genotypes 2 or 3 who do not show a RVR have a rather low SVR. In this setting, an extension of treatment duration to 36-48 weeks might be considered.

Recommendations

1. *Virological response to treatment must be monitored at the 4th, 12th, and 24th weeks of treatment and at the 24th week after treatment is finished, always with the same method* ***(Class II, Level A).***
2. *Treatment of patients with HCV genotype 1 must be for 48 weeks with pegylated interferon alpha 2b 1.5 mg/kg/week s.c. or pegylated interferon alpha 2a 180 mg/kg/week s.c. combined with weight dosed ribavirin 800-1400 mg/day (weight-based dose) (Table 6)* ***(Class I, Level A).***
3. *Patients with HCV genotype 1 with factors predictive of good response and RVR may be treated for 24 weeks* ***(Class I, Level A).***
4. *In slow-responder patients, a treatment for 72 weeks should be considered* ***(Class I, Level B).***
5. *In patients who do not achieve EVR and those that present with detectable viral RNA at 24 weeks, treatment ought to be suspended* ***(Class II, Level A).***

6. *Patients with HCV genotype 2 or 3 must be treated with pegylated interferon plus ribavirin for 24 weeks* ***(Class I, Level A).***
7. *Treatment of patients with HCV genotype 2 or 3 with factors predictive of a good response may be shortened to 16 weeks* ***(Class II, Level A).***
8. *Treatment of patients with HCV genotype 2 or 3 with bad or slow virological response may be prolonged to 36-48 weeks* ***(Class II, Level A).***

APPROACH AND MANAGEMENT OF PATIENTS WITH NORMAL LEVELS OF TRANSAMINASES

Approximately 30% of patients with chronic hepatitis C have persistently normal ALT (PNALT) values. Most of these patients have mild or moderate inflammation and absent or mild fibrosis, which can progress over time determining cirrhosis or hepatocellular carcinoma might be found.[37-43]

AST and ALT elevations normally act as important markers of liver injury. However, the definition of "normal values" is currently subjective because reference ranges vary between laboratories, with values above 40 U/L considered high normal levels. There are also differences between males and females: recent data show that in the healthy population the upper level of normal ALT should be around 30 U/L for men and around 19 U/L for women. Application of these limits would improve the sensitivity of the test for detecting patients with asymptomatic disease, although the specificity would diminish. The definition of PNALT in patients with chronic hepatitis C varies in the literature, but most authors define it as ALT measurements lower than 40 U/L on two or three different occasions separated by at least 1 month in a period of 6 months. Most PNALT patients are women; nearly 50% have a genotype 1 virus and viral RNA titers are significantly lower than in patients with elevated ALT. Although hepatic damage is generally mild and stable over time in patients with PNALT and they maintain a good prognosis, almost 20% to 30% of these patients progress to fibrosis, which is why they have recently been considered adequate candidates for antiviral therapy.

Recommendations

1. *The indications for treatment must be evaluated independently of ALT activity* ***(Class I, Level B).***
2. *Treatment protocols in patients with PNALT must be the same as that used in patients with elevated ALT. Likewise, the SVR to combined treatment is similar to that observed in patients with elevated ALT* ***(Class I, Level B).***
3. *As in other patients, treatment must be individualized and adverse effects, comorbidities, likelihood for therapy response, the viral genotype, and the severity of illness assessed by liver biopsy must be considered before treatment commences* ***(Class I, Level B).***
4. *In PNALT patients in which antiviral treatment is not initiated due to minimal liver disease, ALT levels must be monitored every 6 to 12 months and the possibility of taking serial liver biopsies to evaluate the progression of the disease should be offered to reconsider antiviral therapy* ***(Class I, Level B).***

TREATMENT IN CIRRHOTIC PATIENTS

The main objectives of treatment in cirrhotic patients are to prevent disease complications, allow regression of fibrosis, and avoid reinfection of the graft in those patients who will receive a liver transplantation.

When SVR is evaluated in cirrhotic patients, especially in those with decompensated disease, we observe that it is lower than in those patients with chronic hepatitis without cirrhosis. It has also been described that cirrhotic patients present a higher probability of having treatment complications.

Of patients with Child A cirrhosis, it is reported that almost 30% to 40% have SVR; and patients who do not have SVR have a higher probability of developing HCC and a higher mortality rate.[44]

With respect to treatment benefits, from an evaluation of studies carried out in patients with cirrhosis, we conclude that the SVR is inferior and that the evidence level for treatment success is lower for decompensated cirrhotic patients because of the small response and increased probability of developing complications.

Treatment with pegylated interferon plus ribavirin is clearly indicated in patients with compensated cirrhosis, with the condition that their levels of white cells and platelets allow them to tolerate the decrease induced by the treatment. The therapy may be contraindicated in advanced cirrhotic patients with Child B and C class liver disease, due to possibility of decompensation and death.

Recommendations

1. *Patients with compensated Child A cirrhosis must be referred for evaluation and*

must receive the usual treatment ***(Class I, Level A).***

2. *Patients with Child B cirrhosis awaiting transplantation must be treated if the virus is genotype 2; patients with Child B and C liver disease should be treated after compensation* ***(Class II, Level B).***
3. *Patients with decompensated Child B and C liver disease should be referred to a transplantation unit for evaluation* ***(Class I, level A).***

TREATMENT IN POSTTRANSPLANTATION PATIENTS

Liver transplantation offers an effective treatment that significantly reduces morbidity and mortality among these patients. However, hepatic graft reinfection is universal in posttransplantation patients because of the advanced liver disease related to HCV. Reinfection is almost inevitable in patients with measurable viral RNA subjected to liver transplantation.[45-49] The natural history of hepatitis C is more aggressive after liver transplantation than in immunocompetent patients. Graft cirrhosis has been reported in almost 30% of patients five years after liver transplantation and the survival rate is significantly lower than that in HCV-negative patients.

The aim of antiviral therapy prior to transplantation is to reach an SVR at the moment of transplantation and clearance of viral RNA to prevent recurrence and stop disease progression.[50-52]

A preventive strategy seems attractive because treatment is begun while viral levels remain low and before the graft is damaged and thus would be expected to reach higher SVR rates. Nevertheless, in practice only 40% to 60% of patients are candidates to receive treatment in view of the fact that these patients receive high doses of immunosuppression with its consequent pancytopenia, mild renal dysfunction, and the presence of additional medical conditions during the early posttransplantation phase.[6,47,48,53-56] Monotherapy with interferon or peginterferon is not recommended because of low rates of SVR.[57] Peginterferon combined with ribavirin gives higher response rates, but is not well tolerated in patients in the early posttransplantation phase, so the doses need to be reduced in the majority of cases.

Recommendations

1. *Treatment of HCV in patients who receive a liver transplantation is indicated only in candidate patients with adequate supervision of therapy administration and of adverse effects* ***(Class IIA, Level A).***
2. *The therapeutic regime of choice in posttransplantation patients should be peginterferon with ribavirin* ***(Class IIa, Level B).***
3. *Posttransplantation patients should receive erythropoietin and granulocyte growth factor so that the ribavirin dosage does not need to be reduced* ***(Class I, Level B).***

TREATMENT IN NONRESPONDERS AND RELAPSERS

It is considered that almost 60% of patients treated with standard interferon and ribavirin do not respond to treatment. The numbers are even more concerning for the genotype 1 subgroup, as 60% to 75% of these patients will not respond to therapy, while in the genotype 2 and 3 group of patients, almost 30% to 40% will not respond. The response to therapy with pegylated interferon plus ribavirin varies according to the viral genotype: it has been found that patients with genotype 1a have an SVR rate of 42% to 52%,[30] whereas patients with genotype 2 or 3 have an SVR rate of 76% to 84%. If the viral load does not diminish by 2 logs by the 12th week of treatment, the patient is considered a nonresponder. If the viral load is undetectable at the end of treatment but reappears 6–12 months after the treatment, the patient is considered a relapser.

In nonresponding patients, retreatment with the same therapeutic regime reaches an SVR of less than 5%, so is not recommended. Furthermore, modification of therapy with alternative interferons does not demonstrate sufficient evidence of success.

Although it is probable that patients who relapse will respond to the same treatment as given the first time, it is very probable that they will relapse again. In these patients that relapse, the following therapeutic regimes have been proven effective: pegylated interferon alpha-2b 1.5 mg/kg/week plus ribavirin 800 mg daily, and pegylated interferon 1 mg/kg/week plus ribavirin 1,000 to 2,000 mg a day. However, the SVR is 50% with the former therapy and 32% with the latter.[58]

In a study carried out by Reddy, *et al*., patients received pegylated interferon alpha 2a 180 μg per week plus ribavirin 1,000 to 2,000 mg a day for 48 weeks; higher relapse rates were seen in patients over 50 years (SVR 39%) than in younger patients (SVR 52%).[59] Everson and colleagues also described that another predictive factor for a poor prognosis is advanced fibrosis level and cirrhosis. In non res-

ponder patients re-treated with pegylated interferon alpha 2a the authors found that a significant reduction in SVR rates occurred as disease severity increased.[60]

Recommendations

1. *Retreatment with pegylated interferon plus ribavirin in nonresponders and relapsers should be individualized. Treatment should be stopped if HCV RNA is detectable at 12 weeks at any level.* ***(Class II, Level B).***
2. *Retreatment with pegylated interferon plus ribavirin in nonresponders and relapsers to a previous course of standard interferon plus ribavirin or interferon monotherapy may be intended.* ***(Class II, Level B).***
3. *The next patients are considerate good candidates for re treatment:*
   - *Prior relapse (vs non-response)*
   - *Prior non-adherence (if correctable)*
   - *Previous monotherapy (vs IFN/RBV)*
   - *No cirrhosis*
   - *Genotype 2-3 with low viral load* (***Class II, Level B***).
4. *These patients should be monitored frequently and the therapeutic trial should be intended for at least 12 weeks.* ***(Class II, Level B).***

MANAGEMENT OF HCV INFECTION IN PREGNANT WOMEN

The prevalence of anti-HCV antibodies in pregnant women is similar to that in the general population, and tends to increase in pregnant women with significant risk factors such as IVDU and HIV coinfection. In the absence of cirrhosis and portal hypertension, pregnant women infected with HCV do not have obstetric complications, although there are reports of prematurity, low birth weight, and microcephaly. It is infrequent that women with cirrhosis become pregnant. However, if they do, special care is required because of the possibility of decompensation and worsening of the portal hypertension secondary to the increase in abdominal pressure and in the plasma volume and the secondary coagulopathy that may induce severe hemorrhage during delivery.[61-63] Table 7 shows the indications for screening in pregnant women.

Several studies have shown no evidence that the type of birth influences perinatal transmission.

Table 7. Indications for screening in pregnant women.

- Women with history of blood derivatives transfusion especially before 1992.
- Women with history of IVDU.
- Patients and healthcare workers involved in dialysis programs.
- Women with HIV or HBV infection.
- Sexual partners of patients infected with HIV, HBV, or HCV.
- Women with a history of tattooing and/or piercing.
- Transplantation recipients especially before 1992.
- Women with high levels of transaminases.
- Participants in in vitro fertilization programs with anonymous donors.

Airoldi J, Berghella V. Hepatitis C and pregnancy. *Obst Gynecol Surv* 2006; 61: 10. Plunkett B, Grobman W. Routine hepatitis C virus screening in pregnancy: A cost-effectiveness analysis. *Am J Obst Gynecol* 2005; 192:1153-61.

Likewise, several studies performed on breast-feeding indicate that even though small quantities of HCV are found in breast milk and colostrum, these levels are not sufficient to transmit infection because the virus may be inactivated by gastric juices and the immunological compounds of breast milk.[64-66]

Treatment based on pegylated interferon and ribavirin is contraindicated because of the elevated teratogenicity of the ribavirin and the neurotoxic effect of interferon. Antiviral treatment is not recommended during pregnancy.

Recommendations

1. *Every HCV-infected patient must be counseled to avoid alcohol and to prevent hepatotoxic drug use including medicinal herbs* ***(Class I, Level A).***
2. *Patients who have not been immunized against hepatitis A and B must be vaccinated against these viruses* ***(Class I, Level B).***
3. *Pregnant women with premature membrane rupture over 6 hours or vaginal rupture may receive treatment in order to avoid vertical transmission* ***(Class II, Level B).***

MANAGEMENT OF HCV INFECTION IN CHILDREN

The global prevalence of hepatitis C among children is very low, about 1%, so little is known about this disease. The risk groups correspond principally to children with hematological disorders who received transfusions before 1992, and vertical transmission represents one of the most important routes of transmission. Screening of

anti-HCV in children of HCV-infected mothers must be performed after 18 months of age because of the high rate of antibodies transmitted from the mother within the first months after birth. However, if an early diagnosis of HCV infection is desired, testing for serum HCV RNA may be performed at 1-2 months of age.

Most infected children, regardless of the age at which infection was acquired, become chronically ill. Spontaneous resolution in children seems to be infrequent, although the highest frequency occurs in patients infected with genotype 3.[19,67-70] In children, the disease is classically asymptomatic and characterized by a benign course for approximately two decades. Advanced liver disease is extremely rare among pediatric patients. Because of the slow progress of the disease, children are ideal patients for treatment with the goals of viral clearance, regression or retardation of fibrosis onset, prevention of chronic disease and the development of HCC, and improvement of quality of life. Treatment is considered for patients aged 3–18 years, and studies performed so far support the efficacy of combined treatment with pegylated interferon alpha 2a at doses of 100 mg/m^2/week or pegylated interferon alpha 2b at doses of 60 mg/m^2/week or 1.5 mg/kg/week plus ribavirin at doses of 15 mg/kg/day for 48 weeks.

Recommendations

1. *Diagnosis of HCV in children is performed by the same methods as in adults* ***(Class I, Level B).***
2. *Treatment can be started from the age of 3 years with the same indications as in adults* ***(Class I, Level B).***
3. *Screening for anti-HCV must be considered at 18 months in children born to HCV-infected mothers* ***(Class I, Level B).*** *Testing for HCV RNA may be performed at 1-2 months of age if an earlier diagnosis is desired.*
4. *Treatment is based on combined pegylated interferon alpha 2a at doses of 100 mg/m^2/week or alpha 2b at doses of 60 mg/m^2/week or 1–1.5 mg/kg/week plus ribavirin at doses of 15 mg/kg/day for 48 weeks* ***(Class I, Level B).***

TREATMENT OF HCV-INFECTED PATIENTS WITH KIDNEY DISEASE

Patients with kidney disease may be infected by HCV through hemodialysis (due to contaminated blood, the absence or inadequate disinfection of medical equipment, or sharing vials of heparin)

It has been demonstrated that in HCV-infected patients with kidney dysfunction under treatment with hemodialysis, mortality increases because of

Table 8. Treatment according to stage of renal dysfunction.

Stage	Description	Treatment
1	Kidney damage with conserved or slightly elevated GFR (> 90 mL/min)	Usual combined therapy depending on viral genotype.
2	Kidney damage with mildly affected GFR (60–90 mL/min)	Usual combined therapy depending on viral genotype.
3	Moderately affected GFR (30–59 mL/min)	PegIFNα-2b 1 μg/kg/week; or PegIFNα-2a 135 μg/kg/week + Ribavirin 200–800 mg
4	Severely affected GFR (15–29 mL/min)	PegIFNα-2b 1 μg/kg/week; or PegIFNα-2a 135 μg/kg/week + Ribavirin 200–800 mg
5	Chronic renal failure (GFR < 15 mL/min)	PegIFNα-2b 1 μg/kg/week; or PegIFNα-2a 135 μg/kg/week + Ribavirin 200–800 mg
5D	Dialysis	IFN 2a or 2b 3 mU/3 times per week; or PegIFNα-2b 1 μg/kg/week; or PegIFNα-2a, 135 μg/kg/week + Ribavirin 200–800 mg
*	Cryoglobulinemia	Control of the acute event with immunosuppressants and then: INF2a or 2b 3 mU/3 times per week; or PegIFNα-2b 1 μg/kg/week; or PegIFNα-2a, 135 μg/kg/week + Ribavirin 200–800 mg

IFN: Interferon. GFR: Glomerular filtration rate. Modified from: Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, Management and treatment of Hepatitis C: An update. *Hepatology* 2009; 49(4):1335–74.

progression of the liver damage (cirrhosis and HCC). In addition, individual and transplanted organ survival rates decrease after kidney transplantation.

By contrast, it has been noted that levels of ALT in individuals with chronic kidney failure are only slightly elevated or even normal despite the advanced hepatic damage. Thus, hepatic biopsy is recommended in these patients in order to determine the stage of the hepatic lesion following the same guidelines for the procedure in patients without renal dysfunction. Even though patients with renal disease have a major platelet dysfunction that may favor hemorrhagic states, complications are rarely reported in hemodialyzed patients who undergo hepatic biopsy.

Anti-HCV measurement and HCV-RNA quantification should be completed in all patients before initiation of hemodialysis and before and after kidney transplantation. Likewise, screening must be performed in hemodialyzed patients who present with any spontaneous or unexplained liver damage and in people who suffer a nosocomial exposure to HCV.

The suggested treatment continues to be peginterferon plus ribavirin, even in hemodialyzed patients. However, the grade of kidney dysfunction must be taken into account because both drugs are filtered by the kidney. Ribavirin increases the risk of hemolytic anemia and cannot be removed by hemodialysis, so a lower dose and caution in its administration or even avoiding the administration are recommended when the creatinine clearance is < 50 mL/min (Table 8).

Hepatitis C virus (HCV) infection is a risk factor of a variety of extrahepatic diseases, such as mixed cryoglobulinemia and membranoproliferative glomerulonephritis (MPGN), which is the most common glomerulonephritis. In these cases, treatment is indicated in order to eliminate the antigen-stimulating process, although therapy must be individualized, as ribavirin is contraindicated in individuals with creatinine clearance < 50 mL/min, pegylated interferon is poorly tolerated in end stage renal disease and is contraindicated in renal allograft recipients. In addition, when the autoimmune is process is very active, it must be controlled first with the adequate inmunosuppresive therapy, and once the patient is stabilized, antiviral therapy may be considered.

Recommendations

1. *HCV screening must be carried out in all renal patients under hemodialysis treatment who are considered for kidney transplantation* ***(Class I, Level A).***
2. *A liver biopsy must be considered in all patients on hemodialysis who present with any spontaneous or unexplainable liver damage* ***(Class IIa, Level C).***
3. *The dose and type of treatment need to be based on the stage of renal function measured by the glomerular filtration rate of the patient, and should always begin with the minimum doses* ***(Class IIb, Level B).***
4. *In cases of glomerulonephritis associated to HCV infection, antiviral therapy should be addressed in order to eliminate the antigen stimulated process.* ***(Class IIa, Level C).***

TREATMENT OF ACUTE HEPATITIS

It has been found that treatment of acute episodes of HCV infection not only gives more satisfactory responses, but also prevents chronic infection. In a meta-analysis of 16 studies, it was observed a difference in the risk of evolving to a chronic state after treatment of 49% (95% confidence interval, 33%–65%).

Several studies have also demonstrated a preference for initiating treatment 12 weeks after virus identification, allowing some time for the spontaneous disappearance of the virus in that period (52%–67%). Spontaneous resolution tends to occur in patients with genotype 3, low viral load, female sex, and white ethnicity; black ethnicity, HIV coinfection, and advanced age favor viral persistence and chronic disease.

It has been observed that patients with jaundice and fluctuating viremia seem to benefit from late treatment, whereas patients with HCV genotype 1 and high viral load respond better to early treatment.

There is no consensus about optimal treatment doses. Several studies have found satisfactory responses with monotherapy of interferon at doses of 5 million U/day for a minimum of 8 weeks, or pegylated interferon alpha 2b at doses above 1.2–1.33 mg/kg/week for 12 weeks. Although high doses of interferon seem to have more benefit, there are no studies that show any noteworthy benefit with the combined use of ribavirin or with schemes longer than 12 weeks.

Recommendations

1. *Every patient with acute HCV infection without negative characteristics for spontaneous clearance (genotype 1, black race, HIV coinfection, or*

advanced age) must be under careful surveillance for 12 weeks before initiation of treatment because of the possibility of a spontaneous resolution ***(Class IIa, Level A).***

2. *Treatment ought to be initiated with monotherapy of pegylated interferon 1.2 mg/kg/week for at least 12 weeks or interferon 5 million U/day for a minimum of 8 weeks* ***(Class IIa, Level B).***

TREATMENT OF HCV/HBV COINFECTION

Hepatitis C and B viruses are the most frequent causes of chronic liver disease worldwide and coinfection may occur because they share the same routes of transmission. Coinfection with these two viruses implies a more serious disease because it has a greater risk of progression to HCC than HCV monoinfection. It is calculated that between 9% and 30% of patients with HCV are coinfected with HBV. Several studies have proven that HCV infection may suppress HBV replication, thereby diminishing HBV surface antigen (HBsAg) and core antigen (HBcAg) expression, an effect that is mainly observed in patients with genotype 1 HCV in which HBV diagnosis may be delayed for up to 6 weeks.

Treatment of patients coinfected with HCV and HBV must be considered because of the probability that they will develop cirrhosis and decompensated liver disease.

Liver transplantation should be considered in decompensated patients. Likewise, antiviral treatment must be selected on the basis of serological indices (HBeAg, anti-HBe) and levels of HBV DNA and HCV RNA, in order to know what virus replication is predominating. Several studies have demonstrated that combined therapy with interferon alpha 2b at doses of 6 million units three times per week for 12 weeks, followed by 3 million units three times per week for another 12 weeks plus ribavirin 1,200 mg daily for 24 weeks is effective in these patients. Recent data show that peginterferon alpha 2a (180 mg) weekly for 48 weeks and ribavirin (1,000–1,200 mg) daily is equally effective in patients with HCV monoinfection and in those with chronic HBV/HCV coinfection.[71] Some authors recommend combined therapy with lamivudine at doses of 100 mg daily. Both therapeutic regimens show an adequate clearance response.

Recommendations

1. *Combined treatment with pegylated interferon plus ribavirin and triple antiviral treatments both give similar rates of SVR and are the currently recommended treatment* ***(Class IIa, Level B).***

TREATMENT FOR HCV AND HIV COINFECTION

Approximately 25% of HIV-infected patients are coinfected with HCV. Thus, detection tests for HCV must be performed in every HIV-infected patient and vice versa before beginning treatment, being aware that almost 6% of HIV patients do not develop anti-HCV antibodies, so HCV-RNA quantification is necessary.

Several studies report that only 4% or 5% of HIV-infected patients show spontaneous resolution of their HCV infection and response to treatment is not as fast or as sustained as in patients infected only with HCV. Furthermore, coinfection promotes the development of cirrhosis as much as twice as frequently as monoinfection with HCV; this is why it must be detected in time to initiate treatment that favors antiretroviral therapy.

Currently, the recommendation on treatment is pegylated interferon plus ribavirin for 48 weeks at the same doses used in HCV monoinfection. However, hemolytic anemia caused by ribavirin must be considered because it is more common in patients with this coinfection, especially when antiretroviral treatment includes zidovudine or didanosine. Interaction between didanosine and ribavirin increases risk of lactic acidosis and should be avoided. Interferon, on the other hand, reduces the number of CD4+ cells while maintaining their percentage, so does not favor the development of opportunistic infections. Furthermore, it has been found that patients treated with pegylated interferon show reductions of approximately 0.7 log in HIV-RNA levels.

Recommendations

1. *Every HIV-infected patient ought to be screened for HCV and vice versa* ***(Class IIa, Level A).***
2. *Diagnosis of HCV in HIV-infected patients must be confirmed through HCV-RNA quantification because of the false negatives of anti-HCV antibodies that may occur in this coinfection* ***(Class IIa, Level B).***
3. *At present, treatment with pegylated interferon plus ribavirin for 48 weeks at the same doses used in HCV monoinfected patients is recommended with strict vigilance for adverse effects* ***(Class IIb, Level B).***

4. *Interaction between ribavirin and zidavudine and especially didanosine should be avoided. Patients receiving these antiretroviral drugs should be switched to other therapies before starting treatment for hepatitis C.*

MANAGEMENT OF SIDE EFFECTS OF HEPATITIS C TREATMENT

Although many HCV infections are asymptomatic, there can be side effects to drug administration. Depending on the doses, frequency, or pathway of administration, between 10% and 15% of patients suffer these side effects.

Among the most common symptoms are flu-like symptoms, fatigue, headache, thyroid dysfunction, anorexia, digestive disorders, depression, and anemia. Most of these symptoms are tolerable and are easily controlled with an adjustment in dose or frequency of administration. Unfortunately, 10%–15% of patients drop out of treatment because of these symptoms, which evidently affects the response to antiviral treatment.

Side effects related to the combined use of pegylated interferon plus ribavirin correspond to those produced by the separate components. The most common side effects produced by interferon are flu-like symptoms, fatigue, anorexia, weight loss, alopecia, insomnia, depression, anemia, neutropenia, thrombocytopenia, and Hashimoto thyroiditis. No reports have shown an important difference between side effects of the different interferons. Among the side effects produced by ribavirin, the most frequent is hemolytic anemia and the second most common is pruritus.

In cases of neutropenia (which occurs in about 30% of patients) < 750 cells/mL, the interferon dose must be reduced by half; however, in cases of neutropenia < 500 cells/mL, treatment must be suspended and reinitiated with a half-normal dose once the neutrophil count is restored. In cases of thrombocytopenia (12%), the treatment must, again, be reduced by half if values are < 50,000 cells/mm^3 and suspended at values of < 20,000 cells/mm^3.

Although anemia is common (50%) and completely reversible with the suspension of treatment, when hemoglobin (Hb) levels are < 10 g/dL, ribavirin doses must be reduced by half. If 4 weeks after dose reduction Hb is < 8.5 g/dL, treatment must be suspended. In some cases (Hb < 12 g/dL and no contraindications), erythropoietin can be administered at doses of 40,000 to 60,000 IU/week.

Depression is also common among HCV patients and is common as a side effect (6%), especially among IVDU, alcoholics, and those with multiple comorbidities. A nonhepatotoxic treatment of citalopram 5 mg/day, paroxetin 5–30 mg/day, or sertralin 25–100 mg/day is recommended.

Recommendations

1. *Treatment of side effects should be symptomatic and opportune to avoid treatment dropouts* ***(Class IIa, Level A).***
2. *In cases of anemia of Hb < 10 g/dL, ribavirin doses must be reduced by half and reevaluated in 4*

Table 9. Emerging Therapies for HCV. Specifically targeted antiviral treatment (STAT-C).

Enzyme inhibitors	Genome sequence-based	Others
Protease	RNA interference	Modifications of IFN and ribavirin -Albinterferon -PEGIFN lambda (IL-29) -Taribavirin (viramidine)
Polymerase	Antisense	Immunological -Therapeutic vaccines -Toll-like receptor agonists -Hepatitis C immunoglobulin -Monoclonal antibodies
NS5A		Targeting cellular factors -Cyclophilin antagonists -Nitazoxanide -mIR-122 inhibitors -Entry inhibitors

weeks; in cases where it continues or worsens, treatment should be suspended and erythropoietin must be administered at doses of 40,000–60,000 IU/week ***(Class IIa, Level B).***

3. *In cases of neutropenia with < 750 cells/mL, interferon doses should be reduced by half and suspended if neutrophils < 500 cells/mL. Treatment should be reinitiated at a half-dose once the neutrophil count is restored* ***(Class IIa, Level B).***

   - *A granulocyte colony stimulating factor is recommended for the treatment of neutropenia* ***(Class IIa, Level C).***

4. *In cases of thrombocytopenia < 50,000 cells/mm^3, the interferon dose must be reduced by half or suspended if the count is < 20,000 cells/mm^3* ***(Class IIa, Level B).***
5. *Every patient with depression must be treated with citalopram 5 mg/day, paroxetin 5–30 mg/day, or sertralin 25–100 mg/day to avoid poor compliance with base treatment* ***(Class IIa, Level B).***

NEW APPROACHES TO HCV TREATMENT

HCV therapy is under study in order to improve the response among patients. New options are needed because of the following two situations.

1. *The response to treatment has been shown to depend on viral genotype, viral load, ethnicity, and recently the presence of the IL-28B gene, and it is noted that available therapies have lower efficacy in Latin American patients.*
2. *If disease is mild, patients can wait for better therapies.*
3. *There are several side effects of treatment with pegylated interferon and ribavirin.*

The most advanced drugs in development are the protease and polymerase inhibitors. The protease inhibitors interfere with the translation of HCV and the polymerase inhibitors act by interfering with viral replication (Table 9).

Recent studies have shown that protease inhibitors such as telaprevir or boceprevir, combined with pegylated interferon and ribavirin, achieve efficacy rates of more than 70% in naïve patients with genotype 1 HCV. It has been demonstrated that the efficacy rate for white Latin Americans is around 34%.

The polymerase inhibitors are either analogs or nonnucleoside inhibitors. The nucleoside analogs are active site inhibitors that require conversion to the active triphosphate. The nucleosides affect a highly conserved region of the genome and have a high genetic barrier to resistance. These inhibitors are active against genotypes 2 and 3. None of them is yet available because most are in phase 2 trials.

Recommendations

1. *Those infected with HCV genotype 1 or 4 who are naïve-to-treatment and without advanced liver disease could wait for direct-acting antiviral (DAA) treatment, especially because results from telaprevir- and boceprevir-based triple therapies have shown improved response rates* ***(Class IIa, Level B).***
2. *Those infected with HCV genotype 1 or 4 with significant liver disease should be treated with pegylated interferon and ribavirin. In the case of no response, a triple therapy could be considered* ***(Class IIa, Level C).***

INSULIN RESISTANCE, METABOLIC SYNDROME, AND THEIR IMPLICATIONS IN HCV INFECTION

Insulin resistance (IR), defined as the pathophysiological condition in which higher than normal concentrations of insulin are required to maintain normal levels of glycemia, is closely related to the development of such pathological states as obesity, diabetes mellitus type 2 (DM2), and nonalcoholic fatty liver disease (NAFLD), which is the most frequent hepatopathy in Western countries. Several studies have found that it is present in 30% to 70% of HCV-infected patients and that it increases the risk of developing DM2 in HCV-positive patients.

Hepatic steatosis is present more often in patients with HCV genotype 3, which has been implicated as pathogenic in its development. However, this has given way to the conclusion that in non-genotype 3 HCV, the cause of the steatosis is IR.

In HCV-infected patients, it has been found that the worsening of IR and associated pathologies is caused by effects on the insulin receptor substrates (IRS) and the generation of proinflammatory cytokines. NAFLD is promoted because of the increase in lipogenesis caused by IR and the metabolism of fatty acids.[72] This, in

addition to the proinflammatory state, favors its evolution to steatohepatitis, cirrhosis, and HCC.[73] Clinical repercussions of IR have been demonstrated in several studies in which it was concluded that IR diminishes the response to antiviral treatment independent of the viral genotype, evolution of liver damage and fibrosis, or development of DM2.

Some studies have suggested that reduction of body weight before initiating HCV treatment gives a better response. They have also suggested the use of insulin-sensitizing agents such as pioglitazone and metformin, and although the studies have found some differences that favor late virological response (LVR) or slightly favor SVR, they have failed to find a significant improvement with the use of these agents, for which more studies are needed.[74-76]

Recommendations

1. *All HCV-infected patients must have a metabolic assessment that includes HOMA-IR measurement* ***(Class I, Level A).***
2. *Weight loss ought to be recommended in all HCV-infected patients who are overweight or obese, preferably before initiation of HCV treatment* ***(Class I, Level B).***
3. *Use of insulin-sensitizing agents must be individualized depending on comorbidities* ***(Class IIb, Level B).***

HEPATITIS C AND HEPATOCELLULAR CARCINOMA (HCC)

In several regions of the world (especially in Asia and Africa), a strong association is found between HBV infection, HCV, and alcoholic cirrhosis, and the development of HCC. In Oceania and both North and South America, the last two entities tend to be the principal risk factors in the development of this hepatic neoplasm. Small multicenter studies in some regions of America and Latin America confirm the presence of HCV in patients with HCC.

Several risk factors have been related to the genesis of HCC. The main risk factor in HCV-infected patients is the presence of cirrhosis. Although the incidence is much lower in noncirrhotic patients, there are also other risk factors related to host, virus, and some external factors. For the host, risk factors include advanced age (> 50 years), male sex, thrombocytopenia, esophageal varices, and comorbidities. For viral variables, a controversial meta-analysis showed that patients with HCV genotype 1b have twice the normal risk of developing HCC. Other studies, also meta-analyses, report that active or occult, but not past, HBV infection correlates with the development of this pathology, whereas HIV coinfection promotes the advance to cirrhosis. Finally, for external factors, heavy alcohol intake doubles the possibility of evolution to HCC compared with those who do not drink. Treatment with interferon for any other cause besides hepatitis C acts as protection against the development of HCC.

Recommendations

1. *Every patient with HCV must be monitored because of the risk of developing HCC, especially those with cirrhosis, HBV or HIV coinfection, or chronic alcoholism* ***(Class I, Level A).***
2. *Monitoring must be performed by ultrasonography every 6 months* ***(Class IIa, Level A).***

HEPATITIS C TREATMENT: COST-EFFICACY, COST-BENEFIT

The impact of HCV infection is high and will tend to increase in the future. There are registers in some Latin American countries that suggest that the infection is the second most frequent cause of cirrhosis and that its prevalence will increase to more than 70%. It also favors the evolution of liver disease from the infiltrative stage to inflammatory, necroinflammatory, and neoplasmic stages with their corresponding functional loss and diminishment in quality-adjusted life years.

Objectives of treatment are to eliminate the virus and stop the progression of liver damage. To do so, SVR is valued because it is associated with improvement of liver function, liver histology, and quality of life. Pegylated interferon combined with ribavirin is currently considered the therapy with the best response. Some models indicate that if this treatment were given to 10% of infected patients, a reduction of 6% in morbidity and 4% in mortality would occur, and if it were given to 50% of patients the reductions would be of 26% and 20%, respectively.

Recommendations

1. *Preventive measures must be emphasized and actions directed to minimize risk factors should be taken in order to reduce the incidence of infection* ***(Class I, Level A).***

2. *Every HCV-infected patient must have individualized treatment analyzing his/her predictive and risk factors in order to reduce morbidity and mortality caused by the infection* ***(Class I, Level B).***
3. *Elective treatment for patients with no associated risk factors must be with combined pegylated interferon plus ribavirin* ***(Class I, Level A).***

MEDICAL AND LEGAL IMPLICATIONS OF HEPATITIS C

HCV infection is a worldwide public health issue. There are many routes of transmission that are used to define certain risk groups: patients with a history of blood transfusion before 1992, hemophiliacs, IVDU, patients in treatment with hemodialysis, patients who have had acupuncture, patients with tattoos, patients with multiple sexual partners, newborns to infected mothers, and healthcare workers. Prevalence in this last group, for which healthcare worker–patient, patient–healthcare worker, and patient–patient transmission is a reality, varies from 1% to 10%. The first and second routes occur especially among surgeons who are in direct contact with patient tissues during any intervention; the third route is more obvious given the outbreaks in some hemodialysis centers.

Currently, prevention is considered the main route to avoid viral transmission. Screening of every blood donor and of every patient with documented IV drug use, history of transfusion before 1992, in hemodialysis, or with evidence of hepatopathy is recommended. Use of body protection for healthcare personnel is another recommendation. Not every country recommends routine screening within this group, but usually only after exposure.

There are no regulations to follow post exposure. Each institution follows its own protocol. Generally it is recommended to wash the exposed site (antiseptics and disinfectants have not provided better preventive indexes, but neither are they contraindicated) and to screen both the medical personnel and the patient for HBV, HCV, and HIV. Although there is no indication for suspending normal activities, some countries, such as Germany, do promote it until viral loads of less than 1 x 10^3 IU/mL are reported.

Recommendations

1. *Routine screening of every patient with the following risk factors: hemotransfused before 1992, IVDU, and/or people with multiple sexual partners or with any identified liver disease* ***(Class I, Level A).***
2. *Routine screening of healthcare workers* ***(Class IIb, Level C).***
3. *Use of body protection for medical personnel at every point during which contact is established with exposed patient tissues* ***(Class I, Level A).***
4. *Reinforcement of healthcare personnel education regarding protection and techniques of injection, taking of blood samples, minor surgeries, and other procedures in which they have contact with exposed patients' blood* ***(Class I, Level A).***
5. *In case of exposure of the healthcare worker to patient blood products, the exposure site must be washed with soap and water, and samples for HBV, HCV, and HIV analysis taken for both the healthcare worker and the patient* ***(Class I, Level A).*** *The following steps should be taken:*

   - *Measure ALT activity.*
   - *Follow up with new blood samples of the affected healthcare worker in 4–6 months.*
   - *Confirm diagnosis of HCV with HCV-RNA quantification or anti-HCV by RIBA.*

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