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Latin American Association for the Study of the Liver Recommendations on Treatment of Hepatitis C

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1. INTRODUCTION

Chronic hepatitis C virus (HCV) infection is a major public health concern. It is estimated that more than 185 million people, around 3% of the world population, are currently living with chronic hepatitis C.[1] About one-third of these individuals will develop cirrhosis and hepatocellular carcinoma (HCC), leading to approximately 350,000 deaths each year.[2,3] The prevalence of HCV infection in Latin American countries is heterogeneous, as illustrated in table 1.

In 2010, the Latin American Association for the Study of the Liver (LAASD) developed its own guidelines for the diagnosis and treatment of HCV. Until 2011, the standard of care for patients with HCV genotype (GT)1 was pegylated interferon (PEG-IFN) plus ribavirin (RBV). The sustained virologic response (SVR) rates were 40-50%.[4,5] The standard of care for patients with either HCV GT2 or GT3 was PEG-IFN plus RBV for 24 weeks with SVR rates ranging from 69% to 74%.[6] At that time, first-in-class protease inhibitors (PIs) [boceprevir (BOC) and telaprevir (TVR)] were the first direct-acting antiviral (DAA) therapies approved for patients with GT1, given in conjunction with both PEG-IFN and RBV for 24-48 weeks, depending on whether the patient had a robust response. The first-generation DAAPIs inhibit the NS3/4A protease, which in turn diminishes viral replication. The SVR rates in pivotal phase 3 studies of treatment-naïve patients with GT1 receiving PEG-IFN plus RBV plus a PI ranged from 63 to 75%. In patients who previously received PEG-IFN plus RBV but did not achieve SVR, superior SVR rates of 75-83% were achieved in relapsers, 52-59% in partial responders, and 29-38% in nonresponders.[7-10]

In 2013, the LAASD reviewed and updated the guidelines to include the first-generation DAAs for treatment and laboratory tests for the diagnosis, monitoring and evaluation of patients with chronic HCV infection.[11] Fortunately, thanks to ongoing research, *in vitro* systems to culture HCV became available, and these tools have allowed the development of DAAs that are specifically designed to target HCV proteins, particularly the nonstructural proteins. In fact, the efforts have focused on the six nonstructural (NS) proteins (NS2, NS3, NS4A, NS4B, NS5A, and NS5B) that play critical roles in HCV entry, replication, and proliferation, and serve as possible targets for development of the new DAA therapies (Figure 1).

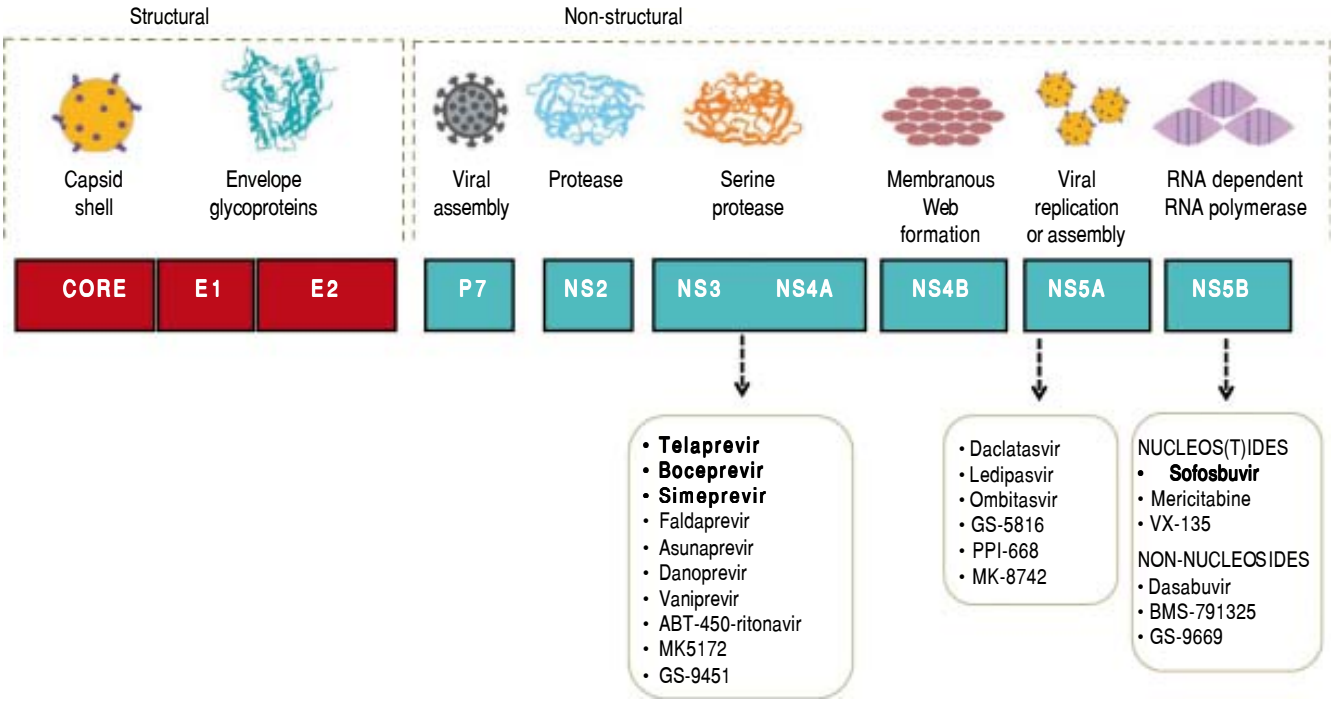

Figure 1. *The six nonstructural (NS) proteins (NS2, NS3, NS4A, NS4B, NS5A, and NS5B) that play critical roles as possible targets for the development the new DAA therapies.*

Table 1. Prevalence and evidentiary support.

Countries & total population in 2005	Prevalence % (95% UI) & numbers of persons with anti-HCV in 2005†	Evidentiary support‡
Caribbean Aruba Anguilla Netherlands Antilles Antigua and Barbuda Bahamas Saint Barthelemy Belize Bermuda Barbados Cuba Cayman islands Dominican Republic Guadeloupe Grenada French Guiana Guyana Haiti Jamaica Saint Kitts and Nevis Saint Lucia Saint Martin Montserrat Martinique Puerto Rico Suriname Turks and Caicos Islands Trinidad and Tobago Saint Vincent and the Grenadines British Virgin Islands US Virgin Islands > 42 million	2.1 (1.6-2.6) > 0.7 million	Very limited
Andean Latin America Perú Ecuador Bolivia > 50 million	2.0 (1.4-2.7) >1.0 million	Very limited
Central Latin America Colombia Costa Rica Guatemala Honduras Mexico Nicaragua Panama El Salvador Venezuela > 216 million	1.6 (1.3-1.9) > 3.4 million	Very limited
Southern Latin America Argentina Chile Uruguay Falkland island > 58 million	1.6 (1.1-2.2) > 0.9 million	Moderate
Tropical Latin America Brazil Paraguay > 193 million	1.2. (1.0–1.4) > 2.3 million	Extensive

† Overall prevalence and numbers of people with anti-HCV estimated by applying age-specific prevalence to IHME age-specific population data 2005. ‡ Extensive: Average of ≥ 5 datapoints per country; moderate: average of 2-4 datapoints per country; limited: average of 1 datapoint per country; very limited: average of <1 datapoint per country.

NS3/4A inhibitors

The NS3/4A inhibitors target the serine protease NS3/4A, which cleaves the HCV polyprotein at four sites. As mentioned above, the first DAAs available were TVR and BOC. The protease inhibitor simeprevir(SMV) has recently been licensed, and others, such as faldaprevir, asunaprevir, vaniprevir, and ritonavir-boosted ABT-450, are currently in the process of being approved. The newer drugs have easier dosing regimens and seem to have a lower propensity for toxicity and drug-drug interactions. In addition, these new DAAs have activity against GTs other than GT1, particularly GT2, GT4, GT5, and GT6. For GT1 infection, PIs can increase the SVR from 45% with standard PEG-IFN-based treatment to as high as 80%-90%, with lower responses typically seen in those with advanced cirrhosis or other markers of poor outcome.

Resistance to PIs occurs mainly through newly acquired resistance mutations in the gene encoding the NS3 protease, at codons 36, 54, 155, 156, 168, and 170.[12] It has also been suggested that the existence of polymorphisms in some viruses, such as the Q80K polymorphism that is present in the GT1a viruses, is associated with a reduced response. Although worldwide prevalence of this polymorphism has been calculated to be 25%,[13] it is associated with about a threefold reduction in response to SMV and a significant reduction in treatment response.[14] The PIs are currently licensed for use in conjunction with PEG-IFN and RBV, although IFN-free regimens (such as combined SMV and sofosbuvir (SOF) and asunaprevir or ABT-450-based treatment) will soon be available.

NS5A

The NS5A protein is essential for both viral assembly and replication. Inhibitors of NS5A are potent antivirals that act at picomolar concentrations, although the response differs between GT1a and GT1b viruses.[15] Daclatasvir(DCV), ledipasvir (LDV), ABT-267, GS-5816, and MK-4782 are NS5A inhibitors that may be licensed within the next year. These agents seem to have minimal adverse reactions, and no serious drug-drug interactions are yet known. Resistance mutations in the NS5A protein encountered in clinical trials to date include M28T, L31M/V, and Y93C/N.

NS5B inhibitors

The NS5B RNA-dependent RNA polymerase is responsible for replication of HCV RNA. As with inhibitors of the HIV reverse transcriptase enzyme, there are two main classes of NS5B inhibitors. These are the nucleos(t)ide inhibitors (nucleoside or nucleotide inhibitors), which bind to the active site of the enzyme and cause premature chain termination, and the nonnucleoside inhibitors, which bind outside the active site but cause a conformational change that inhibits RNA polymerase activity.

Several agents are currently in advanced stages of development, and the nucleos(t)ide inhibitor SOF- recently became the first NS5B inhibitor to be li-

Table 2. Grading system for recommendations.

Classification	Description
Class 1	Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation procedure or treatment is beneficial, useful, and effective.
Class 2	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a diagnostic evaluation, procedure, or treatment.
Class 2a	Weight of evidence/opinion is in favor of usefulness/efficacy
Class 2b	Usefulness/efficacy is less well established by evidence/opinion.
Class 3	Conditions for which there is evidence and/or general agreement that a diagnostic evaluation, procedure, or treatment is not useful/effective and in some cases may be harmful.
Level of evidence	**Description**
Level A	Data derived from multiple randomized clinical trials or meta-analyses.
Level B	Data derived from a single randomized trial or nonrandomized studies.
Level C	Only consensus opinion of experts, case studies, or standard of care.

censed for treatment of HCV infection. These agents seem to have pangenotypic activity and minimal toxicity or drug interactions. *In vitro* resistance to SOF seems to occur with the development of an S282T mutation in the NS5B gene, although this has yet to be seen in large numbers of patients. This is in contrast to PI-based therapy, where resistance mutations are commonly seen when treatment fails.[16]

The LAASD recommendations have been updated in 2014 by a panel of experts chosen by the Governing Board. The Recommendations have been based as far as possible on evidence from existing publications. 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 clinical practice guidelines has been classified into 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 2).

The guidelines are intended for use by hepatologists, gastroenterologists and infectious disease doctors who are in charge of the treatment of people with hepatitis C in the Latin American countries. Also is important to mention that these guidelines might change as new therapies will be introduced in different countries. For that reason, we are planning to review and update them at least one or two times a year.

2. PUBLIC POLICIES FOR FACING HEPATITIS C IN LATIN AMERICAN COUNTRIES

Developing countries face substantial barriers to screening, including low political, provider, and community awareness of hepatitis C as a significant health threat, that leads to deprioritization of testing and other preventive health services. In addition, public health officials in many developing countries do not understand the true burden of disease within their borders because their surveillance infrastructure may be inadequate: one-third of World Health Organization (WHO)member countries do not collect prevalence data for viral hepatitis.[17] Robust surveillance for HCV infection, particularly serosurveillance, is critical for assessing this burden, because many newly infected people are asymptomatic and do not seek care for their infection until years, even decades, after they are infected. Tables 3 and 4 below list those patients eligible to receive antiviral treatment for HCV.

All treatment-naïve and experienced patients with compensated chronic liver disease related to HCV, who are willing to be treated and who have no contraindications to treatment, should be considered for therapy. Treatment should be prioritized in patients with advanced fibrosis (METAVIR score F3 to F4) and in those patients with clinically significant extra-hepatic manifestations (symptomatic cryoglobulinaemia or HCV immune complex nephropathy). Treatment is justified in patients with moderate fibrosis (METAVIR score F2).

In treatment IFN-free, ideally ribavirin-free therapy may also be considered in patients with decompensated cirrhosis.

The burden of disease is critical for decisions about national health policies, and therefore there is a need for accurate estimations globally, regionally and nationally. However, accurate data on the burden of chronic HCV infection are not available in the Latin American region. In the development of treatment programs for HCV infection, building in methods for data collection and recording that allow regular and routine program review will help to facilitate ongoing service feedback and improvement, and will also help to generate evidence regarding the relative benefits and cost-effectiveness of different program strategies.

Table 3. Patients eligible to receive antiviral treatment for HCV.

- Age older than or equal to 18 years.
- HCV-RNA detectable onserum.
- Chronic hepatitis and significant fibrosis (grade 2 or 3) measured by liver biopsy or non invase methods.
- Compensated liver cirrhosis (Child Pugh 5-6 points without history of variceal bleeding, ascites or encephalopathy).
- No hematological and biochemical alterations that preclude the use of PEG-IFN and RBV.
- No contraindications.
- Motivated patient who understand the treatment and its implications.

Table 4. Laboratory characteristics of candidates for HCV treatment.

- Serum bilirubin < 1.5 mg/dL.
- INR < 1.5 .
- Albumin > 3.4 g/dL.
- No ascites, encephalopathy or variceal bleeding.
- Hb > 12 g/dL, neutrophils > 1500 x $10^3/\mu L$ and platelets > 75,000 x $10^3/\mu L$.

Cost of treatment

Although hepatitis C is curable, most patients outside of the developed world, where hepatitis C is a major public health problem, are unable to access treatment. Treatment coverage should be improved not only in resource-limited countries but also in developed countries where less than 20% of HCV-infected patients receive antiviral therapy (AVT). Decreasing the cost of the drugs is urgently required for developing countries as well as developed countries that will not be able to cover all the HCV treatment-related expenses. This goal is feasible but will require the support of pharmaceutical companies, international health agencies and donors, governments and nongovernmental organizations, and the commitment of scientists and physicians. Mechanisms for accelerated access to simplified treatment of HCV infection should be prioritized. The simplification agenda for HCV management will need to take into account the different capacities of different settings. Governments, policymakers and the academic sector are critical to delivering HCV services, implementing surveillance programs, disseminating information and increasing public and provider awareness. Continued involvement of key stakeholders including advocacy and patient groups is also essential to ensure

that vulnerable and underserved populations have appropriate representation. Although patient and provider factors receive the greatest attention, obstacles arising at the government and payer levels are likewise important. In an international study of HCV providers, lack of treatment promotion and insufficient funding were noted as significant government-level barriers. Lack of insurance coverage, high out-of-pocket expenses and excessive paperwork were cited as payer-level barriers.

3. DIAGNOSIS OF CHRONIC HEPATITIS C (SCREENING RECOMMENDATIONS IN GENERAL AND FOR SPECIAL POPULATIONS)

Hepatitis C is currently a public health problem world wide, recognized as a disease of global importance, affecting both industrialized and developing countries.[18-20] To estimate the global consequences of chronic hepatitis C, knowledge of the prevalence of HCV in each country is required. This estimate should be made through population-based studies. However, because in many countries these are not available and the data are scarce, reference is made only to specific groups, including blood donors, illicit drug users, or individuals with high-risk sexual behavior, which do not represent the population as a whole.[21]

The direct determination of the incidence of HCV infection is difficult. Incidence is estimated using available data on the prevalence. Available data suggest that the prevalence of HCV infection is approximately 2-3% worldwide (130-170 million people). Approximately 15-25% of HCV-infected patients progress to cirrhosis, which can occur in about 20-30 years.[22] On assessing the impact of hepatitis C in the United States of America (USA) in a systematic review,[23] it was clear that screening was neglected (70% of those infected were unaware of their status), and it became clear that the prevalence of cirrhosis is increasing and will continue to increase in the next decade, and that HCV infection is a major cause of mortality and liver-related morbidity. HCV infection leads to significant loss of quality of life and is responsible for significant costs in healthcare.

In Europe, HCV is the major cause of cirrhosis, increasing the mortality rate to 1.5-5 times that of the general population, and in cohorts of hospitalized patients, morbidity/mortality is higher. It was also observed that screening is neglected: HCV is considered to be a huge public health problem.[24]

In a study that evaluated the projection of HCV infection in Latin America,[25] it was observed that the prevalence of HCV varies between 1 and 2.3%. The number of diagnosed and treated cases is still low, while there are increasing rates of complications such as progression to cirrhosis and HCC.

In a recent systematic review of 25 articles, in which the burden of hepatitis C in Latin America was evaluated[26] from nine population-based studies, the estimated burden of the infection was 7.8 million individuals (prevalence of infection of 0.9-5.8%). The biggest challenge appears to be located in Mexico and Brazil, where around 4 million people are infected. Specifically in Brazil, a population-based prevalence study of 19,503 individuals, conducted in the major cities of the country and funded by the Ministry of Health/Bureau of Health Surveillance, revealed an overall prevalence of anti-HCV antibodies of 1.38%.[27]

With respect to the costs of HCV, a US study estimated the cost of a patient with HCV to be US $20,961 compared with US $5,451 for controls.[28] The most recent study that assessed the future burden of HCV in the USA, using a model with a dynamic system involving 36 cohorts, indicates that despite a decrease of two-thirds in the prevalence of infection in 2030, there will be an increase in the incidence of cirrhosis (626,500 in 2015), the incidence of decompensated cirrhosis (107,400 in 2019), the incidence of HCC (23,800 in 2018), mortality from liver disease (29,695 in 2019) and cost (9.1 billion dollars in 2024).[29]

Chronic hepatitis C is a disease with high costs for health care institutions, so efforts are needed in screening and early treatment before progression to cirrhosis-actions that reduce costs in managing this condition. In view of this, the reduction in overall mortality and morbidity related to chronic hepatitis C, especially in settings where resources are scarce, should be considered to be a high priority by public health authorities.[21] It isimportant to emphasize thatin mostcountries of Latin America, the true prevalenceof HCVis not known, and screeningis also neglected. In this document, we attempt to providea suggested course of action for the countries of this continent.

The approach to detecting HCV infections is to screen people with a history of exposure to the virus and to test individuals who have an identifiable risk factor. The main risk factors are the following: illicit injecting drug useat present orin the past, including intranasal drug users who share contaminated devices; receipt of blood products before the screening of blood supply started in 1992, although screening was not mandatory until 1996 in Chile; receipt of clotting factor concentrates before 1987 (after which viral inactivation procedures were implemented); healthcare exposure to long-term hemodialysis, needlestick injuries among health care workers, and patient-to-patient transmission resulting from poor infection control practices. Other modes of transmission include children born to HCV-infected mothers and sexual transmission, mainly among HIV-infected men who have unprotected sex with men. Other risk factors include in-

carceration, exposure to an infected sexual partner or multiple sexual partners, and living with HCV-infected people, sharing a razor or toothbrush, and tattooing or piercing in an unregulated setting. Because of shared transmission modes, people with HIV infection are at risk for HCV infection. Recent data also support testing of all cadaveric and living solid-organ donors because of the risk that HCV infection poses to the recipient. Individuals with unexplained elevations of aminotransferases should be tested for the presence of HCV infection.[30-33] Generally, it is accepted that these risk groups should be screened for HCV. In 1998, the Centers for Disease Control and Prevention (CDC) issued recommendations for identifying HCV-infected people.[34] Testing for HCV was recommended for people most likely to be infected, including those who had ever had at least one risk factor. In 1999, HCV testing was recommended for people with HIV.[35]

Given that Brazil is the Latin American country with the largest number of HCV carriers, the analysis of the previously cited population-based study becomes important in evaluating the major risk factors.[27] In this study, the multivariate model showed the following to be predictors of HCV infection: age, injecting drug use (OR = 6.65), inhaled drug use (OR = 2.59), hospitalization (OR = 1.90), groups socially deprived by a lack of sewage disposal (OR = 2.53), and injections with a (reusable) glass syringe (OR = 1.52, with a borderline p value). In another study[36] that had the objective of obtaining data on acute hepatitis C in Brazil, among 133 nonuremic patients, the main risk factors were hospital procedures, whereas in 37 hemodialysis patients, dialysis was the single risk factor in 95% of cases. Also of interest is a study that assessed the prevalence of hepatitis C markers in patients with HIV infection and found almost 40% positivity.[37] Thus, we can infer that the main risk factors described in the literature are also important in Latin American countries, suggesting the importance of screening in these risk population.

However, in the Brazilian population-based study, the known risk factors explain fewer than 50% of the infected cases,[27] limiting the application of prevention strategies. In a study that evaluated participants in the National Health and Nutrition Examination Survey, only 3.7% of HCV-infected people reported having been tested based on known HCV-related risk factors.[38] Thus, the success of risk-based testing strategies has been limited.

It is important to recognize the impact of HCV on liver disease progression, which will impact the health system.[39] In a multicohort natural history model for predicting disease outcomes and benefits of therapy, it was concluded that prevalence of hepatitis C cirrhosis and its complications will continue to increase through the next decade and will mostly affect those older than 60 years of age.[40] Assuming that 30% of cases of HCV are diagnosed and that up to 25% of those are treated, we would expect just a 1% reduction in cirrhosis by 2020, with a 15.6% reduction if all patients were treated. If the success of therapy increased to 80%, treatment of all infected individuals would reduce cirrhosis by 30.4%. This makes it urgent to define innovative public health policies to improve HCV screening, which is the only way to allow more HCV patients access to therapy. Other wise, without screening, HCV patients remain undiagnosed until they develop advanced liver disease. Only with increasing AVT(more diagnoses) and with a higher response rate (a reality in the present era) will we observe a reduction in disease impact in the coming years.

It is estimated that 45%-85% of adults in the USA who are chronically infected with HCV are unaware of their condition.[41] Higher percentages have been reported in European countries,[24] and the figure in Latin America is unknown. However, the reality in Latin America is likely to be similar. Because of the limited effectiveness of the testing recommendations, the CDC, after searching multiple data bases to identify studies pertinent to the question, considered a birth-year-based strategy to increase the proportion of infected individuals detected: one-time HCV testing of all people born during 1945-1965 ("baby boomers"). These people account for around 75% of all prevalence of those with anti-HCV antibodies.[42] European health authorities should encourage innovative approaches, such as those proposed recently by the CDC, to increase the proportion of HCV-infected people aware of their condition.[24] A review that studied 110,223 cases of past or current HCV infection showed that 68% of people would have been identified through a one-time birth-year-based HCV testing strategy, whereas only around 27% would have been screened with the risk-based approach.[43] The cost-effectiveness of birth-cohort testing is comparable to that of current risk-based screening strategies.[41,42]

In the Latin American region, the age-specific prevalence of HCV infection shows the increase progressive with age above 35 years old, with a peak prevalence at age 55-65.[1] This is in concordance with the data from Pereira, *et al*. showing a

progression of HCV prevalence with age.[27] In addition, the prevalence of infection did not vary significantly between 1990 and 2005, suggesting that age (rather than year of birth) is associated with the risk of infection.[1]

Although there is a lack of direct evidence that HCV testing positively affects related morbidity and mortality, targeted testing of people belonging to risk groups and those with high HCV prevalence is likely to increase the number of HCV-infected people identified, referred to a specialist, and provided access to treatment, resulting in a higher likelihood of treatment success. An additional benefit is that knowing one's HCV infection status provides the opportunity to reduce transmission of the disease.

Thus our screening recommendations for general and special populations are as follows.

RECOMMENDATIONS

Screening recommendations
for general and special populations.

1. Individuals who have an identifiable risk factor

- *Illicit injecting drug users at present or in the past and intranasal drug users.*
- *Individuals who received blood products (or underwent an organ transplant) before 1992 and who received clotting factor concentrates before 1987.*

2. Individuals with a history of comorbidities

- *Long-term hemodialysis.*
- *HIV infection.*
- *Unexplained elevations of aminotransferases.*

3. Individuals with a history of exposure to the virus.

- *All people who have undergone a medical procedure.*
- *Needlestick injuries among health care workers.*
- *Needlestick injury and children born to HCV-infected mothers.*
- *Sexual transmission, mainly among HIV-infected men who have unprotected sex with men.*
- *Having been incarcerated.*
- *Exposure to an infected sexual partner or multiple sexual partners.*
- *Living with HCV-infectedpeople, sharing a razor or toothbrush.*
- *Having undergone tattooing or piercing in an unregulated setting.*

(Rating: Class I, Level B).

4. *Given the need to reduce the proportion of infected patients who are unaware of their status, especially in countries with more resources, we also recommend the following.*

- *One-time HCV testing of people 45 years and older.*

(Rating: Class I, Level B).

4. METHODS FOR STAGING LIVER DISEASE IN CHRONIC HEPATITIS C

Staging of liver fibrosis is important in the management of patients with chronic liver diseases, because the severity of fibrosis influences the prognosis and treatment options.[44,45]

Liver biopsy is still the "gold standard" in the diagnosis and staging of chronic hepatitis C because it provides data on staging and disease activity, concomitant liver disease and associated metabolic processes, prognostic assessment and therapeutic monitoring. As liver biopsy is an invasive method, it presents certain risks, including mortality and morbidity (the risk of severe complications is 1/4,000 to 1/10,000). Moreover, it has some limitations, including sampling errors and interobserver disagreement, especially for intermediate degrees of fibrosis.[46-49]

Noninvasive methods used to evaluate the staging of fibrosis have shown good accuracy, and several methods or combinations have been validated and can replace biopsy in clinical practice.

Mechanical noninvasive methods

The four mechanical methods currently available are: transient elastography (liver assessed by FibroScan®), acoustic radiation force elastography (ARFI), shear wave elastography (SWE) and MRI elastography. FibroScan®, ARFI and SWE have in common the fact that they are unable to discriminate between intermediate stages of fibrosis, their best application being for the diagnosis of cirrhosis and advanced fibrosis (F3, F4).[49,50]

Of the four methods mentioned, transient elastography (liver assessed by FibroScan®) is the one associated with the greatest number of publications, especially in chronic hepatitis C, and accordingly is the most validated and standardized for almost all liver diseases.[51-55] It can be performed at bedside with a rapid learning curve, and it has a validated prognostic value in cirrhosis. However, the equipment is expensive, obesity and the presence of ascites are limitations for the procedure, and acute hepatitis, extrahepatic cholestasis, and congestion can lead to false positive results.[50]

ARFI and SWE are more recent and very promising methodologies, associated with the propagation of acoustic waves. In a recent meta-analysis, ARFI gave results comparable to FibroScan® for the diagnosis of cirrhosis and advanced fibrosis,[56] and SWE can have a superior performance for significant fibrosis (≥ F2).[50] Despite this potential, these two methods, compared with FibroScan®, still need better standardization and better knowledge of the confounding factors, and have a longer learning curve.[50] MRE is the least studied and standardized, and the most expensive, of the mechanical methods, but it can have great sensitivity in differentiating intermediate degrees of fibrosis.[57]

Biochemical (biomarkers) and combined methods

Several biochemical tests have been investigated in hepatitis C in an attempt to evaluate the staging of chronic hepatitis C.Among these, the most validated are undoubtedly the noncommerical APRI (AST-to-platelet ratio index) and FIB4 (AST, ALT, age and platelets) and the patented Fibrotest® and Fibrometer®. Fibrometer®, and especially Fibrotest®, have been extensively used in France and other countries, and are validated for use in various liver diseases. These two tests are patented and must be performed in laboratories that meet certain quality standards, and thus are more expensive and less readily available than other tests. The APRI score and FIB4 are simple, reproducible, lower cost and more reliable. Comparative independent studies could not demonstrate significant differences between the different biochemical methods and also pointed out that their performance alone is not adequate to replace liver biopsy[58,59] and that none of them should be recommended as a sole method for staging disease. The exception would be in low- and medium-income countries where the WHO guideline[2] suggested the utilization of APRI and FIB4 for staging of advanced and significant fibrosis. For this purpose, there are three main cutoff values for APRI: < 0.5 for the exclusion and ≥ 1.5 for the confirmation of the presence of significant fibrosis, and < 1.0 and ≥ 2 for the diagnosis of cirrhosis.[2,60] For FIB4, the threshold value would be < 1.45 for excluding significant fibrosis and > 3.25 for confirming cirrhosis.[2,58] The staging strategy proposed by WHO experts uses a combination of the low cutoff to rule out the presence of a particular stage of fibrosis and the high cutoff to confirm that the patient has fibrosis that is greater than or equal to a particular stage (e.g. > F2 or F4).[61]

Although this strategy could have some application, as stated by WHO experts, a significant number of patients will fall in the indeterminate range of test results (i.e., their score will be between

the low and the high cutoffs), and such patients will need an additional method to predict liver fibrosis.[2]

To increase the sensitivity and specificity of noninvasive methods, attempts have been made to combine the methods. The first successful combination was of Fibrotest® with APRI (*SAFE-biopsy*) for the diagnosis of both cirrhosis and a significant biopsy.[60] Alternatively Fibrometer®, Fibrotest® and APRI can be combined with elastography using FibroScan® in diagnostic algorithms.[61-63] With the use of these algorithms, there is an important reduction in the need for a liver biopsy, and a high percentage of cases can be correctly classified.[64,65]

RECOMMENDATIONS

1. *Whenever possible, use noninvasive methods. Liver biopsy in the staging of hepatitis C is reserved for cases of clinical suspicion of association with other liver disease, cases of disagreement between the results of noninvasive methods, or cases where the use of indirect methods is clinically or technically impossible* ***(Class 1, Level A)***.

2. *The assessment of advanced liver fibrosis (F3, F4 of METAVIR classification) and cirrhosis (F4) in patients with chronic hepatitis C can be made indirectly by mechanical methods, preferably by elastography by FibroScan®* ***(Class 1, Level B)***.

3. *The highest accuracy and greatest reduction in the need for liver biopsy is achieved with the combination of two biomarkers or with the combination of a biomarker with a mechanical method* ***(Class 1, Level B)***.

4. *In the setting of low-income countries, the combination of a low and high cutoff level for the APRI and FIB4 levels can be indicated (recommendation 2B) but a significant number of patients will not be properly classified* ***(outside the cutoff values)***.

5. TREATMENT OF CHRONIC HEPATITIS C GT1 WITH DAAs

Sustained eradication of HCV RNA is possible and is associated with higher overall survival, even for patients who already have cirrhosis.[66-70] Remarkably, the success of therapy has increased exponentially with the arrival of new DAAs. The downside is that these new agents have a high cost and are not uniformly available in different parts of the world.[71] Any HCV-infected patient is a potential candidate for antiviral treatment, but the priority should be for those with more advanced fibrosis (METAVIR ≥ F2) and/or clinically significant extrahepatic manifestations associated with HCV.[56,66] Patients with milder disease and no compelling reason to eradicate HCV should probably wait for the IFN-free therapies that will be available in the near future.

Fortunately in some Latin American countries the new DAAs are in the process to be approved a we expect that they can be use in this year.

Finally, it is important to be familiar with all nomenclature and definitions in the medical treatment of hepatitis C (Table 5).

Treatment of HCV GT1 with IFN-based therapy

Treatment-naïve patients

In resource-limited countries, treatment-naïve patients with HCV GT1 usually have access to PEG-IFN/RBV plus one of the first-generation PIs: BOC or TVR. There are no head-to-head trials comparing both agents; however, most recent meta-analyses indicate similar efficacy and safety of both agents (*Grade 1A*).[72,73] Furthermore, about half of the treated patients achieve an extended rapid viral response (eRVR) and are able to use response-guided therapy (RGT) to shorten the treatment duration to 24 weeks of triple therapy without loss of SVR, provided that they are not cirrhotic (*Grade 1A*).[7,8,74] Definitions of eRVR differ for BOC (HCV RNA < 15 IU/mL between weeks 8 and 24) and TVR (HCV RNA < 15 IU/mL at week 4 and 12). Stopping rules also differ for BOC (HCV RNA > 100 IU/mL at week 12 or detectable at week 24) and TVR (HCV RNA above 1,000 IU/mL at week 4 or 12, or detectable at week 24). Thus, the therapeutic scheme recommended with BOC for a noncirrhotic treatment-naïve patient is 4 weeks of PEG-IFN/RBV alone (lead-in) followed by BOC plus PEG-IFN/RBV for 24 weeks in those with eRVR or 44 weeks in those without eRVR.[7] For a noncirrhotic treatment-naïve patient treated with TVR, the recommendation is to start directly with 12 weeks of TVR plus PEG-IFN/RBV followed by 12 weeks of PEG-IFN/RBV in those with eRVR or 36 weeks in those without eRVR.[8,74] Registration trials in HCV GT1 treatment-naïve patients show that triple therapy with either BOC[7] or TVR[8] plus PEG-IFN/RBV has a higher SVR rate than PEG-IFN/RBV alone (66-75% *vs.* 38-44%, respectively) (*Grade 1A*). Overall, the safety of triple therapy was similar to that of PEG-IFN/RBV, with around 10-15% of severe adverse events (SAEs) and < 1% of deaths in both regimens. However, there was a higher incidence of the following adverse events compared with PEG-IFN/RBV alone:[7,8,74]

1. Anemia with TVR and BOC (39-49% *vs.* 19-29%);
2. Disgeusia with BOC (43 *vs.* 18%);
3. Skin rash with TVR (61 *vs.* 48%).

Pruritus and anal discomfort were seen more often with TVR than with BOC.

Pill burden was more of an issue with BOC (4 pills every 8 h) than TVR (2 pills every 8 h[8,74] or 3 pills every 12 h[75]). Anemia is the primary concern with the first-generation DAAs and should be carefully looked for. It is important to assess the cardiovascular status of patients before starting therapy, especially individuals above 50-60 years of age. Those with lower baseline hemoglobin might need weekly follow-up. RBV dose reduction to 500-600 mg/day does not impact SVR, even if carried out when HCV RNA is still detectable. Erythropoietin

Table 5. Treatment responses in hepatitis C virus (HCV) infection.

- Rapid viral response: undetectable HCV RNA at four weeks.
- Early viral response: ≥ 2 log reduction in HCV RNA at 12 weeks.
- End of treatment response: undetectable HCV RNA at the end of treatment.
- Sustained virologic response (at 12 or 24 weeks): undetectable HCV RNA 12 or 24 weeks after completion of treatment.
- Null response: early viral response not achieved.
- Partial response: early viral response achieved, but virus not completely suppressed by week 24.
- Virologic breakthrough: HCV RNA undetectable during treatment, but virus re-emerges while still on treatment.
- Relapse: reappearance of HCV RNA after cessation of treatment.

can be started if hemoglobin falls to < 10 mg/dL. Transfusion can become necessary in around 5% of patients.[7,8,74] TVR-associated rash occurs in approximately 50% of patients and is usually mild or moderate, frequently managed only with antihistamines and topical steroids. Severe rashes or lesions involving > 50% of the body surface require treatment interruption. Once stopped, neither TVR nor BOC can be restarted. Patients should be advised to inform health care personnel about all concomitant medications, and a list of potentially harmful drug-drug interactions is available on internet sites such as Hep-Drug Interactions from the University of Liverpool (http://www.hep-druginteractions.org), among others.

Recently, two second-wave DAA agents were approved in the USA and European Union (EU) and as we mentioned above the new DAAs in some Latin American countries are in the process to be approved soon: the polymerase inhibitor SOF and the PI SMV. The recommended therapeutic scheme with SOF for HCV GT1 treatment-naïve patients is one pill (400 mg) of SOF once daily plus PEG-IFN/RBV for a fixed duration of 12 weeks, with an SVR of 89% in GT1 patients *vs.* 60% estimated for the historical control group in the NEUTRINO trial.[76]The SVR dropped to 82% in HCV cirrhotics (84% in GT1a and 67% in GT1b) (*Grade 1A*). Only 2% interrupted treatment because of SAEs.

The recommended therapeutic scheme with SMV for HCV GT1 treatment-naïve patients consists of one pill (150 mg) of SMV once daily plus PEG-IFN/RBV for 12 weeks, followed by PEG-IFN/RBV for 12 weeks in those with eRVR, defined as HCV RNA < 25 IU/mL at week 4 and undetectable (< 15 IU/mL) at week 12.[69,70] Overall, in the QUEST 1[77] and QUEST 2[78] trials, the SVR was around 80% with triple therapy *vs.* 50% with PEG-IFN/RBV (*Grade 1A*). Almost 90% of patients achieved eRVR and stopped therapy at 24 weeks, with an SVR of about 88%. SVR was < 30% in patients without eRVR, which is probably too low to justify continuing therapy (*Grade 3*). Cirrhotics treated with SMV had a lower SVR rate, between 58 and 65%, in the QUEST 1[77] and QUEST 2[78] trials, respectively. Among HCV GT1a patients with the Q80K variant present at baseline, SVR with SMV plus PEG-IFN/RBV has the same efficacy as PEG-IFN/RBV alone.[77,78] This mutation occurs in around one-third of GT1a patients in North America but seems to be much less frequent in other parts of the world including South America.[79] Current guidelines advise not to use SMV in GT1a patients with the Q80K variant[2,66,67] (*Grade 3*). Discontinuation for adverse events was < 3% in the QUEST-1 and QUEST-2 trials.[77,78] Triple therapy with SMV was associated with some pruritus, mild rash, mild photosensitivity, and a transient and mild elevation in indirect bilirubin levels, without a concomitant rise in aminotransferases.[77,78] Recent guidelines consider SOF plus PEG-IFN/RBV for 12 weeks, if available, to be the treatment of choice for treatment-naïve HCV GT1.[2,66,67] Treatment with SMV but not TVR or BOC[66] plus PEG-IFN/RBV is considered to be a suitable alternative.[2,66,67] (*Grade 3*).

Treatment-experienced patients

Among treatment-experienced patients with HCV GT1, a phase3 trial showed that a 4-week lead-in with PEG-IFN/RBV followed by 34-44 weeks of BOC plus PEG-IFN/RBV (depending on eRVR) had a higher SVR than PEG-IFN/RBV for 48 weeks, both in relapsers (69-75% *vs.* 29%, respectively) and partial responders (40-52% *vs.* 7%, respectively) (*Grade 1A*).[9] Null responders were not included in this study. Similarly, TVR plus PEG-IFN/RBV for 12 weeks followed by PEG-IFN/RBV for 36 weeks showed a higher SVR rate compared with PEG-IFN/RBV for 48 weeks in all groups of patients, including relapsers (83 *vs.* 24%, respectively), partial responders (59 *vs.* 15%, respectively) and null responders (29 *vs.* 5%, respectively) (*Grade 1A*).[80] A lead-in arm was tested in this study and did not show a higher SVR rate compared with no lead-in (*Grade 1A*). The same stopping rules used for treatment-naïve patients were applied for the treatment-experienced patients (*Grade 1A*). Lead-in could be used in the management of nonresponder patients who are not willing to wait for better therapies. Indeed, if HCV RNA drops > 1 log IU/mL compared with baseline at the end of the lead-in (week 4), the chance of an SVR increases to about 50%, *vs.* only 5% in those with < 1 log IU/mL drop (*Grade 2*).[9,80] Overall, the safety of triple therapy in treatment-experienced patients was similar to that reported in treatment-naïve patients.

Regarding the second-wave agents, there are no phase 3 data available exploring the use of SOF plus PEG-IFN/RBV. Even though SOF + PEG-IFN/RBV has not been studied in patients who previously failed PEG-IFN/RBV(and probably never will be), an exploratory analysis by the FDA shows that approximately 78% of HCV GT1 patients who had previ-

ously failed PEG-IFN/RBV would have responded to SOF plus PEG-IFN/RBV. Alternatively, SMV plus PEG-IFN/RBV for 12 weeks followed by 12 or 36 weeks of PEG-IFN/RBV (depending on eRVR) showed around 80% SVR in relapsers and 50% in previous nonresponders to PEG-IFN/RBV (*Grade 1A*).[10,81] Safety was similar to that reported in treatment-naïve patients (*Grade 1A*).[10,80]

Treatment of HCV GT1 with IFN-free therapy

The COSMOS study is a phase 2 trial that explored the use of 12 or 24 weeks of fixed therapy with SMV (150 mg once daily) plus SOF (400 mg once daily) ± RBV, in two cohorts of HCV GT1-infected patients: prior null responders with METAVIR F0-2 (Cohort 1)[81] and prior null responders and treatment-naïve patients with METAVIR F3-4 (Cohort 2).[82-83] In Cohort 1, the SVR rate was similar in all treatment arms, ranging from 79 to 96%, with no significant advantage of RBV use or longer treatment duration (*Grade 2A*). In Cohort 2, SVR was also similar among treatment arms, ranging from 93 to 100%, with no significant advantage of RBV use or longer treatment duration (*Grade 2A*). Safety was remarkably good, with less than 2% SAEs. This regimen, although based on phase2 trials with low numbers of patients, is being currently recommended in the most recent guidelines as the treatment of choice for patients with HCV GT1 who are ineligible for or previous nonresponders to IFN-based therapy (*Grade 2A*).[2,67]

RECOMMENDATIONS FOR HCV GT1 TREATMENT

A) Current standard of care with PEG-IFN-based therapy

1. *Dual therapy with PEG-IFN/RBV is suboptimal for most patients with genotype 1, except for a small subgroup of patients with IL28B CC, minimal fibrosis and RVR. Therefore, triple therapy is superior to dual therapy with PEG-IFN/RBV and should be preferred in countries where it is available* ***(Class I, Level A)***.

2. *Patients with mild fibrosis and without extrahepatic manifestations could wait for IFN-free therapy and should be followed closely to make sure that there is no rapid disease progression* ***(Class II, Level B)***.

3. *Treatment with TVR plus PEG-IFN/RBV should be stopped if HCV RNA is > 1,000 IU/mL at weeks 4 or 12 or detectable at week 24* ***(Class I, Level A)***.

4. *Treatment with BOC plus PEG-IFN/RBV should be stopped if HCV RNA is > 1,000 IU/mL at week 8 or > 100 IU/mL at week 12 or detectable at week 24* ***(Class I, Level A)***.

5. *Giving TVR or BOC to treatment-naïve patients who have eRVR and fibrosis METAVIR stage < F3 could shorten triple therapy to 24 weeks based on response-guided therapy* ***(Class I, Level B)***.

6. *SOF plus PEG-IFN/RBV for 12 weeks is superior to triple therapy with TVR or BOC and should be preferred in countries where it is available* ***(Class II, Level B)***.

7. *SMV plus PEG-IFN/RBV for 24 weeks in patients with eRVR is superior to triple therapy with TVR or BOC in patients with GT1b or GT1a without the Q80K variant and could be an alternative option in countries where SOF is not available* ***(Class II, Level B)***.

8. *Treatment-experienced patients with null or partial response to PEG-IFN/RBV have low rates of SVR with PEG-IFN-based therapies, especially if METAVIR F3/F4. Therefore, patients should preferably wait for IFN-free therapy. If treatment with TVR or BOC is contemplated, it is recommended to start with a lead-in phase and to proceed with triple therapy only if HCV RNA drops > 1 log at week 4 of dual therapy* ***(Class II, Level B)***.

B) Current standard of care with IFN-free therapy

9. *Phase 3 results with SOF plus SMV for 12 weeks or SOF plus DCV for 12 weeks are still pending. Based on phase 2 data, these regimens could be recommended for patients who either are IFN ineligible or have had null or partial response to PEG-IFN/RBV* ***(Class II, Level A)***.

10. *SOF plus DCV for 12-24 weeks is preferable in patients who failed triple therapy with TVR or BOC, because there is no reliable evidence that SOF plus SMV can be used in patients that failed a regimen with a protease inhibitor* ***(Class III, Level B)***.

11. *Phase 3 data showing SVR above 80% with short duration therapy are already available for several combinations of new DAA compunds, such as SOF plus LDV co-formulated in a single pill, ABT-450/r/ombitasvir plus dasabuvir, and asunaprevir plus daclatasvir (for genotype 1b); however, at the time of this writing, these have not been approved, so they will be reviewed in the future when this guideline is updated.*

6. RECOMMENDATIONS FOR HCV GT2 TREATMENT

HCVGT2 accounts for nearly 10% of the patients with chronic HCV worldwide. Until recently, the combination of PEG-IFN and RBV was considered to be the standard therapy for patients chronically infected with GT2 HCV.[84] This regimen is associated with the best rates of SVRcompared with other GT, reaching 85%. However, this protocol has many adverse effects, and there are patients who are unable to be treated with PEG-IFN and patients who have previously failed to obtain an SVR with standard therapy. The DAAs TVR and BOC are approved for use only for GT1. An alternative treatment is necessary, and one potential option is the second-generation DAAs, which showed activity across all GTs in *in vitro* studies.

DAAs TVR is an oral nucleotide analogue inhibitor of the HCV-specific NS5B polymerase enzyme, which has shown pangenotypic activity *in vitro*. Two randomized, phase 3 studies were conducted in patients with chronic hepatitis C GT2 or GT3 infection. In both studies, SOF and RBV were administered orally at a dose of 400 mg once daily and 800-1,200 mg twice daily, respectively. In the first trial, named POSITRON, the safety and efficacy of SOF+RBV over 12 weeks was compared blind with that of placebo in patients unable to receive PEG-IFN. The overall SVR rate was 78 *vs*. 0% ($p < 0.001$). The SVR rate was 93% among patients with GT2 infection. This high SVR rate was similar when cirrhosis was diagnosed. In the second study (FUSION), 201 patients who had failed prior treatment were randomized to receive 12 or 16 weeks of treatment. HCV GT2 infections were significantly associated with a high SVR rate with both treatment durations (86 and 94% respectively). Cirrhotic patients had 60 SVR when they received 12 weeks of treatment and 78% SVR with 16 weeks (compared with 96 *vs*. 100% in the patients without cirrhosis).[85]

No patient receiving SOF in either study had virologic breakthrough, and among the patients who had a relapse, sequencing analysis of samples collected at the time of relapse showed no resistance-associated variants (RAVs).

Regarding safety, the rates of SAEs in the POSITRON trial were 5% in the SOF plus RBV group and 3% in the placebo group; in the FUSION study, the rates were 5% in the 12-weeks group and 3% in the 16-weeks group. Patients treated with SOF and RBV had higher rates of fatigue, insomnia and anemia compared with those who received placebo.

Zeuzem, *et al*.[86] conducted a study involving HCV GT2 and GT3 (treatment-naïve and previously treated patients) that confirmed the efficacy described above. The HCV GT2 group was randomized to receive SOF plus RBV or placebo for 12 weeks. AnSVR was obtained in 68 of 73 treated patients. The rates of response were consistently high across subgroups. The absence of virological breakthrough during treatment and the absence of RAVs in relapse confirm thatthe SOF plus RBV regimen has a high barrier to resistance.The reasons for the higher rates of response among patients with HCV GT2, also observed among patients treated with PEG-IFN/RBV, remain unclear.

LDV demonstrated a high potency for HCV GT1a, GT1b, GT4a, and GT6a but lower activity against GT2a and GT3a.[87]

In vitro, DCV is an oral highly selective NS5A inhibitor of HCV replication with broad coverage of HCV GTs. The combination of DCVplus SOF given for 24 weeks achieved an SVR in 91% of treatment-naïve patients infected with HCV GT2/GT3. Addition of RBV had no effect on the SVR rate.[88]

This treatment is well tolerated, has comfortable administration,short treatment duration and excellent efficacy. The expected high cost of this treatment will preclude its prompt and wider use, allowing room for alternative cheaper options in this easier-to-treat population. Access is currently the most important limitation on this treatment.

RECOMMENDATION

1. *Combination of daily SOF (400 mg) and daily RBV (1,000 or 1,200 mg in patients < 75 kg or > 75 kg, respectively) for 12 weeks is recommended in treatment-naïve patients and treatment-experienced noncirrhotic patients* ***(Class 1, Level A)***.
2. *Extended treatment should be considered in cirrhotic nonresponder patients* ***(Class 1, Level B)***.
3. *If there are no contraindications, PEG-IFN/RBV may be considered to be an acceptable treatment until SOF becomes available and accessible* ***(Class 1, Level A)***.

7. TREATMENT OF CHRONIC HEPATITIS C GT3 WITH DAAs

Overall, it is estimated that about 10-15% of the world HCV reservoir is accounted for by GT3.[89] The approved treatment for chronic HVC GT3 in South America is still PEG-IFN/RBV for 24 weeks with a reported SVR rate before the addition of PIs of 69%, far lower than for GT2-infected patients (82%) but higher than for those with GT1 (45%-50%).[4,90,91] A better understanding of the HCV life cycle has led to the development of a number of new DAAs.[92]

DAAs associated with IFN-containing regimens

TVR and BOC are an important breakthrough for hepatitis C GT1 treatment, increasing SVR rates in treatment-naïve patients from 44 to 70%.[93,94] Unfortunately, in GT3 patients, BOC monotherapy achieved only a modest drop in HCV RNA levels, while the activity of TVR was negligible.[95,96]

Patients treated with DCV plus PEG-IFN for 12 or 16 weeks achieved numerically higher SVR rates than those treated with PEG-IFN/RBV alone, with the SVR rate being lower in GT3 than GT2 patients (68 *vs*. 83%, respectively).[97] Because this difference was not statistically significant, this combination was not studied further for GT3.

In the ELECTRON study, a combination of SOF (400 mg once daily) and RBV for 12 weeks plus PEG-IFN (4, 8 or 12 weeks of therapy) resulted in a 100% SVR at week 12 in a small group of noncirrhotic GT2 and GT3 patients.[98] In a similar study (PROTON), patients with GT2 or GT3 without cirrhosis who received SOF plus PEG-IFN/RBV for 12 weeks achieved an SVR12 rate of 92% (23/25 patients).[99] The LONESTAR-2 study evaluated SOF plus standard of care for 12 weeks in GT3 treatment-experienced individuals: the reported SVR was 83% (20/24), including 10/12 patients with cirrhosis.[100]

DAAs with IFN-free regimens

A noninferiority phase 3 study, the FISSION trial, included treatment-naïveGT2 and GT3 patients and compared SVR rates between SOF and RBV for 12 weeks with standard treatment with PEG-IFN/RBV for 24 weeks.[101] Although the SVR12 rates were similar for both groups (67%), SVR rates were significantly lower for GT3 than for GT2 (58 *vs*. 97%; respectively). Furthermore, in GT3 patients, SVR rates in the SOF arm were even lower than in the standard-of-care arm (58 *vs*. 62%, respectively, p = NS).[101]

Similar findings were described in the FUSION and POSITRON trials. These studies evaluated SOF and RBV for 12 or 16 weeks in prior nonresponders (FUSION) and patients intolerant to IFN (POSITRON).[102] Again, SVR rates were consistently lower in GT3 than in GT2 patients. Cirrhosis was associated with even lower SVR12 rates: 60 and 19% in GT2 and GT3, respectively.[102] Extending therapy with SOF and RBV from 12 to 16 weeks increased overall SVR rates from 86 to 94% in GT2 patients and from 30 to 62% in GT3 patients. Notably, in the subgroup of patients with cirrhosis and GT3, prolonging therapy from 12 to 16 weeks tripled SVR12 rates from 19 to 61%.[102] Thus, with the intention of improving SVR rates in this difficult-to-treat population, the VALENCE study evaluated SOF/RBV therapy for 24 weeks in GT3 patients. The overall SVR12 was 84% and was higher among treatment-naïve patients than among treatment-experienced patients (93 *vs*. 77%, respectively). In treatment-experienced noncirrhotic and cirrhotic patients, the SVR12 rates were 87 and 60%, respectively.[103]

In more recent open-label study,GT2 and GT3 patients who had failed 12- or 16-week SOF/RBV regimens (FISSION, FUSION and POSITRON) were offered either SOF/RBV for 24 weeks or SOF/PEG-IFN/RBV for 12 weeks. Retreatment with SOF regimens of longer duration or with the addition of PEG-IFN resulted in SVR12s of 63% (24/38) and 91% (20/22), respectively.[103]

Two phase 2 trials evaluated the association of SOF with two different NS5A inhibitors. Firstly, the ELECTRON-2 trial evaluated the combination of SOF with LDV ± RBV for 12 weeks in treatment-naïve GT3 patients. The addition of RBV to SOF/LDV resulted in a 100% SVR12, while the SOF/LDV group showed 64% SVR12.[104] Secondly, GS-5816 25 mg or 100 mg was associated with SOF in GT1-GT6 treatment-naïve noncirrhotic patients. The SVR12 in GT3 patients was 93% in both groups (25/27).[105]

Recently, a study evaluated the combination of DCV and SOF in an IFN-free regimen in previously untreated patients with GT1, GT2 or GT3.[106] The patients were randomly assigned to receive DCV plus SOF ± RBV for 24 weeks. A total of 89% (16/18 patients) with GT3 infection had an SVR12. The most common adverse events were fatigue, headache and nausea. The addition of RBV did not affect the virological response rate and increased the frequency of anemia.[106]

In summary, hepatitis C GT3 infection has become one of the most difficult to treat. It is now debatable whether GT2 and GT3 patients should be combined in clinical trials because of their distinct characteristics. Few data are available to define the best treatment option for this population. In Latin America, the combination of SOF with RBVfor 24 weeks seems to be the best alternative for noncirrhotic HCV GT3 patients, once SOF becomes approved. In IFN-tolerant patients who have failed a previous SOF-RBV regimen and in treatment-naïve patients with cirrhosis, therapy with SOF/PEG-IFN/RBV may be considered to be the best alternative. More effective approaches such as SOF/DCV or SOF/LDV plus RBV may not be alternatives because of their prohibitive cost. In the meantime, while we wait for approval of new DAAs, the combination of PEG-IFN/RBV remains an acceptable standard of care.[67]

RECOMMENDATIONS FOR GT3 HCV INFECTION

A) Current standard of care with PEG-IFN and RBV

1. *Treatment duration should be personalized according to the on-treatment virological response at weeks 4 and 12 and eventually week 24* ***(Class I, Level B).***

2. *Treatment should be stopped at week 12 if the HCV RNA decrease is < 2 log^{10} IU/mL and at week 24 if HCV RNA is still detectable* ***(Class I, Level B)****.*

3. *In patients with an RVR and low baseline viral load (< 400,000-800,000 IU/mL) and absence of negative predictors of response (advanced fibrosis, metabolic syndrome, insulin resistance or hepatic steatosis), treatment for 12-16 weeks can be considered* ***(Class II, Level B)****.*

4. *Patients who have an early virologic response (HCV RNA detectable at week 4 but undetectable at week 12) should be treated for 48 weeks* ***(Class II, Level C)****.*

B) DAAs with or without PEG-IFN and/or RBV

1. *Weight-based RBV (1,000 or 1,200 mg in patients < 75 kg or ≥ 75 kg, respectively), and daily SOF (400 mg) for 24 weeks. This alternative should be proposed in treatment-naïve noncirrhotic patients* ***(Class II, Level A)****.*

2. *PEG-IFN-a, weight-based RBV (1,000 or 1,200 mg in patients < 75 kg or ≥ 75 kg, respectively), and daily SOF (400 mg) for 12 weeks* ***(Class II, Level A)****. This regimen is especially recommended in treatment-experienced and cirrhotic patients.*

3. *Combination of daily SOF (400 mg) and change to "new combinations of SOF plus NS5A inhibitors such as DCV and or LDV with or without RBV should also be considered in the future".*

4. *PEG-IFN/RBV remains an acceptable standard of careuntil SOF and new direct antiviral agents are approved.*

8. TREATMENT OF CHRONIC HEPATITIS C GT4, GT5 AND GT6 WITH DAAs

Epidemiology

Although they account for more than 20% of all HCV cases worldwide, GT4, GT5 and GT6 have generally been neglected or underrepresented in most large multinational clinical trials.[107]

New treatment options for HCV GT4 (Table 6)

Four to six treatment options are suggested for the management of patients infected with HCV GT4.[66,67]

- Treatment-naïve patients can be managed with a combination of weekly PEG-IFN, daily weight-based RBV (1,000 or 1,200 mg in patients < 75 kg or ≥ 75 kg, respectively) and daily SOF (400 mg) for 12 weeks *(recommendation B1;* ***Class IIa, Level B****)*.
- Patients who are PEG-IFN intolerant/ineligible can be treated with daily SOF (400 mg) and daily weight-based RBV (1,000 or 1,200 mg in patients < 75 kg or ≥ 75 kg, respectively) for 24 weeks *(recommendation C2;* ***Class IIb, Level B****)*.
- One alternative consists of a combination of weekly PEG-IFN, daily weight-based RBV 1,000 or 1,200 mg in patients < 75 kg or ≥ 75 kg, respectively) and daily SMV (150 mg) *(recommendation B1;* ***Class IIb, Level B****)*.
- SMV should be administered for 12 weeks in combination with PEG-IFN and RBV, followed by PEG-IFN + RBV for an additional 12 weeks (total treatment duration 24 weeks) in treatment-naïve and prior relapser patients. However, an additional 36 weeks with PEG-IFN + RBV (total treatment duration 48 weeks) should be administered in prior partial and null responders, including cirrhotics *(recommendation B1)*. HCV RNA levels should be monitored on treatment because therapy could be shortened if HCV RNA level is ≤ 25 IU/mL at treatment week 4, week 12 and week 24 *(recommendation A2)*.
- Although there are no data with the next combination, but extrapolating the results of the COSMOS trial, in patients with HCV GT4, an IFN-free combination of daily SOF (400 mg) and daily SMV (150 mg) for 12 weeks *(recommendation B2)*, adding daily weight-based RBV (1,000 or 1,200 mg in patients < 75 kg or ≥ 75 kg, respectively), should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior nonresponders and/or patients with cirrhosis) *(recommendation B2)*.[67]

Table 6. Trials of treatment for HCV genotypes 4, 5 & 6.

Hepatitis C genotype 4 Study	Authors	Number of patients	SVR (%)	Drugs
NEUTRINO Phase III trial	Lawitz E, *et al*.	28 treatment-naïve patients	96	PEG-IFN + RBV + SOF
RESTORE trial	Moreno, *et al.*	35 treatment-naïve patients,	89	
		22 prior relapsers,	86	
		10 prior partial responders	100	
		and 30 prior null responders	75	PEG-IFN + RBV + SMV
COMMAND-1	Hezode C, *et al.*	12	100	PEG-IFN + RBV + DCV
American patients of Egyptian ancestry	Ruane PJ, *et al.*	14 treatment -naïve patients	79/100 at 4 and 12 weeks	
		15-17 treatment-experienced patients	59/93% at 4 and 12 weeks	SOF+ RBV
Hepatitis C genotype 5 & 6				
NEUTRINO Phase III trial	Lawitz E, *et al.*	1 patient with HCV G-5 and 6 patients with HCV G-6	100	PEG-IFN + RBV + SOF

- We can consider that patients infected with GT4 can be treated with an IFN-free combination of daily SOF (400 mg) and daily DCV (60 mg) for 12 weeks in treatment-naïve patients or 24 weeks in treatment-experienced patients (pending data with 12 weeks of therapy in treatment-experienced patients) *(recommendation B2)*. Adding daily weight-based RBV (1,000 or 1,200 mg in patients < 75 kg or ≥ 75 kg, respectively) should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior nonresponders and/or patients with cirrhosis *(recommendation B2)*.[67]
- An alternative option is the combination of PEG-IFN, daily weight-based RBV (1,000 or 1,200 mg in patients < 75 kg or ≥ 75 kg, respectively) and daily DCV (60 mg) for 12 weeks followed by 12 weeks of PEG-IFN/RBV alone or a further 12 weeks of PEG-IFN/RBV + DCV (response-guided therapy) *(recommendation B1)*.
- DCV should be administered for 12 weeks in combination with PEG-IFN/RBV. DCV should be continued in combination with PEG-IFN/RBV for an additional 12 weeks (total duration of 24 weeks) in patients who do not achieve an HCV RNA level < 25 IU/mL at week 4 and undetectable at week 10. PEG-IFN/RBV should be continued alone between week 12 and 24 (total duration of 24 weeks) in patients who achieve an HCV RNA level < 25 IU/mL at week 4 and undetectable at week 10 *(recommendation B1)*.[67]
- For previously nonresponsive GT4 patients, daily SOF (400 mg) plus weekly PEG-IFN and daily weight-based RBV (1,000 or 1,200 mg in patients < 75 kg or ≥ 75 kg, respectively) for 12 weeks has been recommended for retreatment of IFN-eligible subjects ***(Class IIa, Level C)***. The alternative retreatment regimen for this type of patients could be daily SOF (400 mg) and weight-based RBV (1,000 or 1,200 mg in patients < 75 kg or ≥ 75 kg, respectively) for 24 weeks ***(Class IIa, Level B)***.[66]

Treatment regimen for patients in Latin America with GT4

Although the prevalence of this GT in Latin America is very low, and the experience is limited to isolated cases, the recommendations that could be followed according to the most available drugs in our region are as follows.[26]

- The standard regimen for treatment-naïve patients with GT4 is a combination of subcutaneous weekly PEG-IFN (PEG-IFN-α2a at a dose of 180 μg/week or PEG-IFN-α2b at a dose of 1.5 μg/kg/week) plus RBV at 15 mg/kg/day in two divided doses for 48 weeks *(recommendation A1)*;[26] however, in patients who achieve RVR and who do not have predictors of poor response (baseline viral load > 800,000 IU/mL, advanced fibrosis or cirrhosis and insulin resistance), an international panel of experts suggests that treatment can be shortened to 24 weeks.[26]
- Patients with a complete early virological response (EVR) at week 12 have a high probability of achieving an SVR with a 48-week regimen. Patients with a partial or slow EVR (no RVR and detectable HCV RNA but > 2 $\log^{10}$ drop at week 12 and virus negative at week 24) may be considered for treatment prolongation to 72 weeks, if they can tolerate this.[26]

New treatments for HCV GT5 and GT6 (Table 6)

The following treatment regimens for GT5 and GT6 can be suggested.

- Treatment-naïve patients infected with HCV GT5 or GT6 must be treated with a combination of weekly PEG-IFN, daily weight-based RBV (1,000 or 1,200 mg in patients < 75 kg or ≥ 75 kg, respectively), and daily SOF (400 mg) for 12 weeks *(recommendation B1;* ***Class IIa, Level B****)*.[66,67]
- Patients who are PEG-IFN intolerant or ineligible can be treated with daily SOF (400 mg) and daily weight-based RBV (1,000 or 1,200 mg in patients < 75 kg or ≥ 75 kg, respectively) for 24 weeks *(recommendation C2)*.[67]
- The recommended regimen for HCV GT5 or GT6PEG-IFN/RBV nonresponder patients is daily SOF (400 mg) for 12 weeks and daily weight-based RBV (1,000 or 1,200 mg in patients < 75 kg or ≥ 75 kg, respectively) plus weekly PEG-IFN for 12 weeks also recommended for retreatment of IFN-eligible people (***Class IIa, Level C)***.[67]

Treatment regimen for patients in Latin America with GT5 or GT6

As with GT4, experience with GT5 and GT6 is very limited in our region. However, we can use the following recommendations.[25,26]

- The standard regimen for treatment-naïve patients is the combination of subcutaneous weekly (PEG-IFN-α2a at a dose of 180 μg/week or PEG-IFN-α2b at a dose of 1.5 μg/kg/week) plus RBV at 15 mg/kg/day in two divided doses for 48 weeks *(recommendation A1)*.[26,66,67]

9. TREATMENT OF ACUTE HEPATITIS IN ADULTS

Acute hepatitis C infection is defined as the presence of clinical signs and symptoms of hepatitis within 6 months of presumed HCV exposure.[108] The majority of these patients go undetected. Acute HCV infection accounts for 15% of symptomatic cases of acute liver disease.[109,110] Early treatment is appropriate for patients who do not spontaneously clear the virus, and is associated with high SVR-rates.

Diagnosis

A newly positive HCV RNA polymerase chain reaction (PCR), followed by the development of HCV antibodies within 12 weeks, is considered to be definitive proof of acute infection with HCV. However, this requires documentation of a recent serum sample with a negative HCV RNA PCR and anti-HCV antibodies. In its absence, distinguishing between an acute and a newly discovered chronic infection is difficult, because both cases may have detectable HCV RNA andanti-HCV antibodies. Any patient with symptoms of, or exposure to, HCV should be tested for HCV RNA and anti-HCV antibodies.

HCV RNA

This can be detected by PCR within a period between a few days and 8 weeks postexposure, depending upon the size of the inoculum.[111,112] The minimal interval after which a persistently negative HCV PCR test excludes infection has not been established. In a study of 14 patients with needlestick injuries, a negative HCV PCR at 2 weeks post exposure had a 100% negative predictive value.[113] Most experts recommend testing at baseline, week 4, week 12, and 6 months.

Anti-HCV antibodies

Most patients seroconvert between 2 and 6 months after exposure. The rate is higher in symptomatic infection, where up to half have detectable antibodies at presentation, while in subclinical infection,it may take a year for antibodies to be detectable.[112,114]People with suspected acute HCV or known exposure to HCV must have HCV RNA testing by PCR, because a negative antibody test does not rule out infection.[115] A positive anti-HCV antibody test does not distinguish acute or early infection from chronic infection or from a prior infection that has spontaneously cleared. Some patients with prior infection may have negative antibody tests because anti-HCV antibody levels may drop to undetectable levels in patients who have cleared the infection.[116-118]

Aminotransferase

The level of aminotransferase can fluctuate; elevations of greater than 10-20 times the upper limit of normal are seen, but not all patients will have these at the time of presentation, and normalization of aminotransferase levels after acute infection does not necessarily mean that the infection has cleared.[119,120]

Acute *vs.* chronic infection

This distinction is important because it has treatment implications, as patients with acute HCV infection who do not spontaneously clear the virus should receive treatment with an IFN-based regimen. Treatment decisions and regimen in patients with chronic hepatitis C are very different.

Spontaneous viral clearance

Between 14% and 50% of patients with HCV may spontaneously clear the virus.[112,121] Recent studies report spontaneous clearance rates of around 50%.[36,122-125] Most patients who are destined to clear HCV viremiaspontaneously do so within 12 weeks, and usually no later than 20 weeks, after the onset of symptoms.[121,122] However, clearance after follow-up (12 months) has also been described.[123] Symptomatic acute HCV infection is associated with a higher rate of spontaneous clearance than asymptomatic infection.[121,123-125] Other factors associated with spontaneous clearance include a rapid decline in HCV RNA,[126-130] female sex,[131] and polymorphisms in the *IL28B* gene. Patients who clear HCV should have subsequent HCV RNA determinations at 3-month intervals for 1 year.

Treatment

Most patients with acute HCV will develop chronic infection if left untreated. Treatment with an IFN-based regimen during the acute infection leads to SVR rates over 80%.[132] Not all patients need

treatment, and treatment efficacy depends on several factors.

Who to treat

Treatment should be administered to patients with acute HCV who have a high likelihood of being compliant with treatment, as noncompliance is associated with significantly decreased SVR rates,[133-135] and to those patients who do not have any comorbid illnesses that are contraindications to treatment.

When to treat

The treatment for symptomatic acute HCV should be delayed for 12 weeks from the time of suspected inoculation, or from the time of diagnosis if the time of inoculation is uncertain, to allow spontaneous clearance to occur. One meta-analysis of 1,075 patients suggested overall SVR rates greater than 80%,[132] while a second meta-analysis of 12 trials concluded that delaying therapy by 8-12 weeks did not decrease the SVR rate.[136]

Patients infected *via* a blood transfusion and patients with asymptomatic acute HCV should be offered immediate treatment upon diagnosis, because chronic infection appears to be highly likely. The Hep-Net Acute HCV-III study demonstrated that the efficacy of therapy initiated after waiting 12 weeks to evaluate potential HCV clearance might not be inferior to immediate therapy. However, this strategy requires strict compliance of patients with a follow-up test and, if needed, with therapy. In an intention-to-treat analysis of symptomatic patients, the SVR rate (including sustained spontaneous clearance in the delayed group) was higher with immediate treatment than with delayed treatment (67 *vs.* 54%). This difference was not statistically significant. Among those that completed the treatment and follow-up, the SVR rates were 90 and 93% for the immediate-treatment and delayed-treatment groups, respectively.[135]

What to treat with

- ***PEG-IFN.*** Patients should receive weekly PEG-IFN-α, either PEG-IFN-α2a 180 μg/week or PEG-IFN-α2b 1.5 μg/kg/week. The reported efficacy is from 57 to 95%.[134,137-140]
- ***Standard IFN.*** Standard IFN, 5 million units per day for the first 4 weeks then 5 million units 3 times a week for the remainder of the treatment is an alternative, with an efficacy of 22-98%.[128,132,141] PEG-IFN may be preferable because is easier to use and more tolerable, but head-to-head comparative studies are lacking.
- ***RBV.*** RBV does not appear to be beneficial in patients who are not coinfected with HIV,[142,143] unless is not clear whether their infection is acute or chronic,or in patients with acute infection with positive HCR RNA at the end of IFN monotherapy. Patients who are coinfected with HIV should receive PEG-IFN as well as weight-based RBV (< 75 kg, 1,000 mg; ≥ 75 kg, 1,200 mg) divided into two daily doses, provided there is no contraindication to using RBV. The efficacy of monotherapy in coinfected patients ranges from 0% to 10%.[144,145] The addition of RBV increases the SVR rates to 47-80%.[146-149]
- ***DAAs*** are the standard of care, in combination with RBV with or without PEG-IFNdepending on the GT, for chronic HCV infection in those countries where these agents are available. It is not standard of care for acute HCV infection to use them as first-line therapy because of the high SVR rates with IFN-based monotherapy, the risk of additional side effects with the additional agent, especially with the first generation of DAAs, and the limited data available for the use of these agents in acute infection. A study of the use of TVR in patients coinfected with HIV was published recently.[150] Other studies evaluating the use of IFN-free antiviral regimens are underway.

How long to treat

GT and RVR are the most important factors determining the length of treatment. The duration for GT1 should be 24 weeks, but 12 weeks is a reasonable alternative in patients who have achieved RVR and are not tolerating therapy. For GT2, GT3, and GT4, the duration of therapy is 12 weeks.[151] In patients with GT1 who achieve RVR, the SVR rates are 46, 75, and 92% with 8, 12, and 24 weeks of treatment,respectively, whereas response rates are 0, 0, and 33%, respectively, among those who failed to achieve an RVR. Similar results were seen in patients with GT4.

RECOMMENDATIONS

1. *Symptomatic patients should wait 12 weeks from the time of suspected inoculation or time of diagnosis if the time of inoculation is unknown before starting therapy, to allow time for spontaneous viral clearance to occur* ***(Grade 2B)****. Asymptomatic patients, those infected by blood transfusion and those who are not willing to wait for follow-up testing should be offered immediate therapy* ***(Grade 2B)****. IFN-based monotherapy is the treatment of choice for those HIV-negative patients who fail to clear the virus spontaneously after 12 weeks of follow-up, rather than following these patients closely* ***(Grade 1A)****.*

2. *Patients should receive PEG-IFN(α2a or α2b) rather than standard IFN* ***(Grade 2C)****.*

3. *HIV-negative patients with acute HCV who fail to clear the virus spontaneously and are treatment candidates should receive treatment with an IFN-based regimen rather than combination therapy with IFN and RBV* ***(Grade 2B)****. The addition ofRBV is a reasonable alternative if it is not clear whether the patient's infection is acute or chronic, or if they are HCV RNA-positive after 12 weeks of therapy* ***(Grade 2B)****. The addition of a DAA should be considered in those places where it is available.*

4. *HIV-positive patients with acute HCV who fail to clear the virus spontaneously and are treatment candidates should receive treatment rather than being followed closely* ***(Grade 2C)****. The treatment should be with IFN-based therapy combined with weight-based RBV* ***(Grade 2C)****.*

5. *Patients with GT2, GT3, or GT4 and RVR should be treated for 12 weeks rather than 24 weeks* ***(Grade 2B)****. Those patients with GT1 who do not achieve RVR should be treated for 24 weeks* ***(Grade 2B)****, and those who do achieve RVR should also be treated for 24 weeks rather than 12 weeks* ***(Grade 2B)****.*

10. TREATMENT OF COMPENSATED CIRRHOSIS

Patients with HCV-related cirrhosis face a high risk of developing HCC, end-stage liver disease and the necessity of liver transplantation (LT). Therefore, patients with compensated cirrhosis need to be cured of their chronic HCV infection with some degree of urgency.

In a large and heterogeneous region like Latin America, where in most countries the new-generation DAAs have not yet been approved, we have to consider the use of triple therapy with first-generation PIssuch as BOC and TVR for patients with compensated cirrhosis.

GT1

Real-life studies with the first-generation PIs have demonstrated that GT1 cirrhotic patients, usually nonresponders to previous PEG-IFN/RBV treatment, have high adverse event rates and poor SVR rates.[152,153] In the CUPIC study, among patients given TVR, 74.2% of relapsers, 40.0% of partial responders, and 19.4% of null responders achieved SVR12. Among those given BOC, 53.9% of relapsers, 38.3% of partial responders and none of the null responders achieved SVR12. In a multivariate analysis, factors associated with SVR12 included prior treatment response, no lead-in phase, HCV GT1b (*vs.* GT1a), and baseline platelet count greater than 100,000/mm^3. SAEs occurred in 49.9% of cases, including liver decompensation, severe infections in 10.4%, and death in 2.2%. In multivariate analysis, a baseline serum albumin level less than 35 g/L and baseline platelet counts of 100,000/mm^3 or less predicted severe side effects or death.[152]

In another cohort of 160 GT1 cirrhotic patients, 47% with Child-Pugh (CP) ≥ 6 cirrhosis (CP range 6-10), and 35% previous null/partial responders, received triple therapy for a targeted duration of 48 weeks. SVR12 was achieved by 35% of patients with CP ≥ 6 *vs.* 54% of those with CP = 5. CP = 5, RVR and GT1b independently predicted SVR12. Compared with those with CP = 5, patients with CP ≥ 6 had more PEG-IFN dose reductions, eltrombopag use, transfusions and hospitalizations to manage adverse events. Overall, 42% discontinued treatment early. Nine patients on the waiting list were treated for a median of 97 days prior to LT, and five achieved post-LT SVR.[153]

In addition, many cirrhotic patients are poor candidates for IFN-based regimens.

GT2 and GT3

Refer to the Latin American Association for the Study of the Liver Practice Guidelines: Diagnosis, management, and treatment of Hepatitis C, 2010.[154]

Countries where SOF and SMV are available

Recently, the first nucleotide analogue NS5B polymerase inhibitor, SOF, and a second-generation once-daily dosing HCV NS3/4A inhibitor SMV, were approved in Europe and the USA.

In the phase 3 NEUTRINO study, the SVR12 in treatment-naïveGT1 patients treated with SOFplus PEG-IFN/RBV for 12 weeks was 90%.[76] In the subgroup of cirrhotic patients (17%) included in the study, the SVR rate was 80%, a good response rate compared with previous studies with first-generation DAAs. Unlike observations with the PI-based regimens, the SVR rate in GT1a patients was 98% compared with 82% in GT1b patients. The NEUTRINO study did not include previous null responders, but an FDA analysis estimated an SVR rate in such patients of approximately 70%.

In the phase 3 QUEST 1 study, treatment-naïveGT1 patients were randomized to receive SMV (150 mg) or placebo for 12 weeks plus PEG-IFN/RBV for 24 or 48 weeks according to RGT. The SVR12 rate for cirrhotic patients (12% of the total population) was 58%, compared with 80% in the overall population. The SVR12 rate for GT1b patients was 90%, compared with 71% in GT1a patients.[155]

QUEST 2 was a phase 3 trial with the same design,based on the European population. The rate of SVR12 for cirrhotic patients (11.2% of the total population) was 64.7% compared with 81.3% in the overall population.[156] The SVR12 rate in GT1b patients was 82% compared with 80.4% in GT1a patients. The presence of the Q80K mutation detected in the GT1a subtype reduced the SVR rate from 84% to 58%. Although very common in the US and European population, this RAV appears to be less common in the PI-naïve population in Latin America.[157]

In a phase 2 study of relapsers from previous PEG-IFN/RBV treatment (PROMISE), 260 patients (15.6% cirrhotics) were treated with SMV (150 mg) or placebo for 12 weeks plus PEG-IFN/RBV for 24 or 48 weeks according to RGT. The SVR12 rate for cirrhotic patients was 74.4% compared with 79.2%

in the overall population. The SVR12 rate for GT1b patients was 85.3% compared with 70.3% in GT1a patients.[158]

The combination of SOF plus SMV with or without RBV for 12 and 24 weeks was compared in the COSMOS study in 87 treatment-naïve patients and previous null responders with GT1 HCV infection and advanced (METAVIR F3-F4) fibrosis.[159] SVR12 was seen in 100% of treatment-naïve patients. In the null responders group, SVR12 was 100% with triple therapy and 93% in the group without the addition of RBV.

In the near future, the best chance for a potential cure for patients with cirrhosis is an oral combination regimen of potent DAAs. A new class of HCV DAAs called NS5A inhibitors will be an important part of two potent IFN-free regimens: the once-daily, single tablet, fixed-dose combination of SOF/LDV and a three-drug regimen that includes a fixed-dose combination of a ritonavir-boosted HCV PI (ABT-450) plus ombitasvir (NS5A inhibitor) plus dasabuvir (a nonnucleoside polymerase inhibitor).

Three studies evaluated GT2 treatment-naïve patients with cirrhosis with SOF and RBV for 12 weeks. In the POSITRON study, 207 patients in whom IFN treatment was not an option received SOF with RBV for 12 weeks.[102] Overall, SVR12 occurred in 92% of GT2 patients and in 94% of cirrhotic patients, suggesting that cirrhosis was not a negative predictive factor in this subgroup of patients.

The FUSION study compared 12 and 16 weeks of SOFwith RBV for treatment-experienced patients.[102] Among patients with cirrhosis who received 12 weeks of treatment, the rate of response in GT2 patients was 60%, compared with 96% in noncirrhotic patients. In the arm in which patients received 16 weeks of treatment, the SVR12 was 78% for cirrhotic patients, compared with 100% for patients without cirrhosis.

In the VALENCE study, 73 GT2 patients were treated for 12 weeks with SOF and RBV.[86] Overall, an SVR12 was seen in 93% of these patients, with no significant difference between patients with or without cirrhosis.

An open-label, single-arm phase 2 trial (LONESTAR) evaluated the use of SOF with PEG-IFNand RBV in treatment-experienced patients with HCV GT2 or GT3.[160] Cirrhosis was present at baseline in 61% of patients. AnSVR12 was seen in 96% of 23 patients with GT2. SVR12 occurred in 93% of patients with cirrhosis and in 100% without cirrhosis. Despite the limitations of this small study, combination PEG-IFN plus SOF and RBV is an alternative 12-week regimen for GT2 patients with cirrhosis.

In the POSITRON study, among patients with cirrhosis who received 12 weeks of treatment with SOF and RBV, the rate of response was 21%, compared with 68% among patients without cirrhosis.[102] Among patients with cirrhosis who received 16 weeks of treatment, the rate of response was 66% (78% with HCV GT2 infection and 61% with HCV GT3 infection) compared with 76% among patients without cirrhosis (100% with HCV GT2 infection and 63% with HCV GT3 infection).

In the FUSION study, among patients with cirrhosis who received 12 weeks of treatment, the rate of response in GT3 patients was 19%, compared with 37% in noncirrhotic patients.[102] In the arm in which patients received 16 weeks of treatment, the SVR12 was 61% for cirrhotic patients, compared with 63% among patients without cirrhosis.

In the VALENCE study, 250 GT3 patients were treated for 24 weeks with SOF and RBV.[86] Overall, anSVR12 was seen in 85% of these patients, in 61% of patients with cirrhosis andin 91% of patients without cirrhosis.

In the same single-arm phase 2 trial (LONESTAR) evaluated the use of SOFwith PEG-IFN/RBV in treatment-experienced patients with HCV GT2 or GT3.[160] Cirrhosis was present at baseline in 61% of patients. SVR12 was seen in 83% of 24 patients with GT3. SVR12 occurred in 83% of patients with cirrhosis. Despite the limitations of this small study, a combination of PEG-IFN plus SOF and RBV is an alternative 12-week regimen for GT3 patients with cirrhosis.

RECOMMENDATIONS

Patients with hepatitis C GT1-current

TVR for 12 weeks plus PEG-IFN/RBV for 48 weeks (recommendation A). BOC for 44 weeks plus PEG-IFN/RBV for 48 weeks ***(Class I, Level A, Class I, Level A)****.*

GT1-Current and future

SOF plus PEG-IFN/RBV for 12 weeks (recommendation A). SMV for 12 weeks plus PEG-IFN/RBV for 24-48 weeks (recommendation A). SOFplus RBV for 12 weeks (recommendation B). SOF plus SMV and RBV for 12 weeks ***(Class II, Level A, Class II, Level A, Class II, Level B, Class II, Level B).***

GT2

SOF plus RBV for 12 weeks (recommendation A). SOF plus RBV for 24 weeks ***(recommendation B)****. SOF plus PEG-IFN/RBV for 12 weeks* ***(Class II, Level A, Class II, Level B, Class II, Level B)****.*

GT3

SOF plus RBV for 24 weeks (recommendation A). SOF plus PEG-IFN/RBV for 12 weeks ***(Class II, Level A)****.*

11. TREATMENT OF HEPATITIS C IN PATIENTS WAITING FOR LIVER TRANSPLANTATION

Current AVT in patients awaiting Liver Transplantation IFN-free regimens in patients awaiting Liver Transplantation.

Infection of the graft with HCV after LT is universal in patients who are transplanted for HCV cirrhosis. The course of the HCV recurrence is accelerated, with development of cirrhosis in approximately 30 % of recipients at 5 years.[161] There is a need to treat hepatitis C infection in patients on the waiting list to prevent HCV infection of the graft. Therapy for a short period may achieve undetectable levels of HCV RNA at the time of LT. This strategy may prevent graft infection following LT.[162] Moreover, a second potential benefit of AVT in these patients is to improve liver function (which in some cases might lead to the patient's being delisted). Although this has been clearly shown in patients with HBV-related cirrhosis treated with nucleo(s)tide analogues,[163] information on HCV-infected cirrhotics is lacking.

Patients with advanced cirrhosis awaiting an LT are one of the most difficult populations to treat. Current data on AVT before LT, including the role of new DAA agents, will be reviewed.

Current AVT in patients awaiting LT

Current IFN-based treatments are not optimal in patients with advanced liver disease. PEG-IFN/RBV is indicated for patients on the waiting list and can prevent graft infection in patients who achieve undetectable levels of HCV RNA.[164–166] Response rates are higher in individuals infected with HCV GT2 and GT3 compared with GT1, or in those with the IL28B CC GT. In those patients who achieve viral clearance, a longer duration of treatment is associated with lower rates of HCV recurrence after LT. Nevertheless, IFN-based therapy can only be administered in cirrhotics with good liver function. Good candidates are patients with CP < 7 in whom the indication for transplantation is HCC. In patients with more advanced disease, SAEs (e.g., bacterial infections including spontaneous bacterial peritonitis) can be life-threatening. Thus, only a small proportion of HCV-infected patients can undergo IFN-based therapy, and fewer than 30% will achieve a virological response that is maintained after LT.

The development of the two first-generation PIs, BOC and TVR, has been a major step forward in the treatment of chronic hepatitis C.[9,10,167,168] Unfortunately, response rates are lower in cirrhotic patients, particularly in those who are previous null responders (a frequent situation in patients awaiting LT).

Verna *et al*. reported the results of triple therapy in 20 HCV GT1 cirrhotic patients on the waiting list.[169] Most of them were previous nonresponders and had HCC. Patients underwent triple therapy (90% with TVR) for a median time of 14 weeks; at week 12, up to 77% of patients had undetectable HCV RNA. Seven of the eight patients transplanted by the time of the analysis reached LT with undetectable HCV RNA, and six patients remained RNAnegative 12 weeks after transplantation.

From a safety point of view, 25% of patients discontinued therapy, and two patients were hospitalized because of liver decompensation.

PI-based regimens in patients with compensated cirrhosis may be associated with SAEs such as severe infections, clinical decompensation and even death. These SAEs were not reported in the registration trials because patients included in these studies were compensated cirrhotics without significant portal hypertension. The main predictive factors for severe complications in cirrhotics undergoing triple therapy are a low platelet count (< 100,000/mm^3) and low serum albumin levels (< 35 g/L). The risk for severe complications is 50% in patients with both factors.[168] Overall, the data reported in these studies indicate that the proportion of patients on the transplant waiting list that may benefit from triple therapy is very small.

In summary, current IFN-based regimens are only indicated in patients with compensated liver disease with a good chance of achieving a virological response (i.e., GT2/3 or GT1 IL28B CC, preferably those who are treatment naïve or relapsers from previous PEG-IFN/RBV therapy).

IFN-free regimens in patients awaiting LT

Recently, the first data on the safety and efficacy of IFN-free regimens in patients awaiting LT have been presented. In most phase 2 and registration trials, the proportion of patients with cirrhosis included is relatively small, and most of these are treatment naïve. A significant proportion of patients on the transplant waiting list are treatment experienced (some with a first-generation PI in triple ther-

apy), and most of them have clinically significant portal hypertension. Despite these differences, we decided that it was relevant to review the efficacy data for IFN-free regimens, including those for patients with cirrhosis.

The first oral IFN-free regimen studied in patients awaiting LT combined SOF and RBV.[170] In this phase-2 open-label study, 61 patients received therapy until the time of transplant, or up to 48 weeks of treatment before LT while on the waiting list (median duration 17 weeks). Forty patients underwent LT, and of these, 37 (92%) had HCV RNA < 25 IU/mL before LT. Of these, 26 individuals reached 12 weeks of follow-up after transplantation, and 18 (69%) achieved SVR12. Seven patients (27%) had a virological relapse. Safety and tolerance of this regimen was good. The probability of relapse after LT was closely related to the length of virus undetectability before LT was performed. The most frequently reported adverse events were mild and were attributed to RBV. These results are encouraging and suggest that most likely longer treatment duration and/or the addition of a second DAA, or other combinations, will be able to prevent graft infection in most patients.

Other ongoing studies in GT1 patients with compensated and decompensated cirrhosis will provide results soon.[171] These studies are being performed in treatment-naïve and treatment-experienced patients, combining SOF plus LDV, SOF plus SMV, SOF plus DCV or ABT-450 boosted with ritonavir plus ABT-267 and ABT-333. Some of these combinations are coadministered with RBV, and the duration of therapy is 12-24 weeks. Despite the small sample size, the results are excellent, with SVR12 rates ranging between 90 and 100%. Therefore, the future for these patients is highly promising.

There are some issues that should be taken into consideration in patients awaiting LT. First, the goal in these patients is to achieve undetectable HCV RNA at the time of transplantation. Because the main source of viral production will be removed (liver explant), a short treatment course may be enough to prevent graft infection. In any case, a minimum duration of undetectable HCV RNA before transplantation will be necessary to prevent graft infection, and this will depend on viral kinetics. In most of these treatment combinations, RVR rates ranged from 90 to 100%. These studies are limited by their small size, but they support the potential efficacy of a short-course treatment before LT to prevent graft infection. Nevertheless, studies in patients with significant portal hypertension are crucial, because first- and second-phase HCV RNA decay in these patients may differ from that in patients with early cirrhosis.

A second distinct feature of patients with advanced liver disease is the impact of liver function on drug pharmacokinetics (PK). Liver metabolic functions are significantly involved in the clearance of several drugs. As an example, when SOF is administered, patients with moderate and severe hepatic impairment experience a less profound viral decline than those with normal liver function. These data might have clinical consequences and might explain why, in patients with advanced liver disease, longer treatment duration can reduce the rates of virological relapse.

A third distinct feature of patients awaiting LT is the potential risk of viral breakthrough or relapse during or after treatment, which may theoretically induce flares that could lead to liver decompensation. It is thus very important to choose the best treatment combination (high potency and high genetic barrier to resistance) to minimize the possibility of virological relapse or the selection of RAVs.

Finally, another aim of AVTin patients with decompensated cirrhosis should be improvement of liver function. Preliminary data from the post-LT compassionate use program using SOF and RBV strongly suggest that viral clearance is associated with a rapid improvement in liver function.

RECOMMENDATIONS

- *In patients awaiting LT, AVT is highly recommended, because it may prevent graft infection if HCV RNA has been undetectable prior to transplantation* ***(recommendation A1)****.*
- *In patients with preserved liver function (Child-Pugh A with HCC), therapy with PEG-IFN/RBV might be indicated in patients with GT2 or GT3. Triple therapy including BOC or TVR should only be used in patients with platelets > 100,000/mm^3 and albumin levels > 3.5 g/dL.*
- *Treatment including weight-based RBV (1,000 or 1,200 mg in patients < 75 kg or ≥ 75 kg, respectively) and SOF (400 mg) until LTis indicated if SOF is available* ***(recommendation A1)****.*
- *Patients with preserved liver function (Child-Pugh A) can also be treated with a combination of weekly PEG-IFN-α, daily weight-based RBV (1,000 or 1,200 mg in patients < 75 kg or ≥ 75 kg, respectively) and daily SOF (400 mg) for 12 weeks* ***(recommendation B1)****.*
- *Patients with preserved liver function (Child-Pugh A) and preserved renal function with GT1-4 infection can be treated with daily SOF (400 mg) and daily DCV (60 mg) for 12 weeks prior to transplantation* ***(recommendation B1)****.*

12. POST-LT RECURRENCE

HCV infection is one of the leading causes of end-stage liver disease and the main indication for LT in most countries.[172] All patients who undergo LT with detectable serum HCV RNA experience graft reinfection. Between 20 and 30% of patients have developed cirrhosis at 5 years post-LT.[173] The outcome for transplant patients with cirrhosis of the graft is severe, with a rate of decompensation at 1 year of approximately 40%.[174] Meanwhile 2-8% of patients experience a severe HCV recurrence known as cholestatic hepatitis (CH).[175] In these conditions, the prognosis is very poor for patients who do not respond to AVT, retransplantation being the only option in patients with decompensated liver disease. Because preventive therapy is lacking, the prognosis of HCV-infected LT patients, whose survival is shorter than other recipients, can only be changed by the treatment of recurrent infection.[161] An SVR is associated with better long-term outcomes, improved graft fibrosis and survival.[176] Two approaches can be considered for the timing of AVT after LT: treatment before the development of injury to the graft in the early phase within 1 month after transplantation (preemptive strategy), or treatment when chronic hepatitis has been diagnosed. At present, the preemptive strategy with PEG-IFN/RBV is not recommended, because several studies have shown that it is difficult to initiate AVT with IFN during the postoperative period and that efficacy is poor.[177-181] Patients with severe end-stage liver disease prior to LT are frequently ineligible for this approach. However, the preemptive strategy should be reassessed with the availability of new DAAs. It is generally accepted that AVT should be initiated in the presence of histologically proven HCV recurrence. However, this decision must also take into account the patient's age and general condition, and the stage of fibrosis, usually > F1 on the METAVIR scale. AVT should be initiated in the presence of severe fibrosis and rapid progression of fibrosis with a higher risk of graft loss, especially CH. If a liver graft biopsy is not performed, other noninvasive markers can help to make the treatment decision. A cutoff value of 8.7 kPa for liver stiffness had a sensitivity and a negative predictive value > 0.90 for significant fibrosis and portal hypertension in all cases.[182] Also, it is possible to use the measurement of the hepatic venous pressure gradient, where a gradient > 6 mmHg indicates significant fibrosis.[183] Although noninvasive markers can discriminate the stage of fibrosis, scheduled protocol biopsies of the graft before AVT are essential for obtaining crucial data such as the progression of graft fibrosis, the presence of rejection or biliary obstruction, or the degree of steatosis. However, the tolerance to therapy decreases significantly in patients with fibrosis stage > 3, suggesting that AVT should be initiated before advanced fibrosis develops.[176] Systematic reviews of dual therapy have shown that dose reductions of RBV and/or PEG-IFN were necessary in around 70% of patients, and the rate of treatment discontinuation was approximately 30%.[184-186] Liver recipients are particularly exposed

Table 7. ALEH recommended regimens for treatment of recurrent HCV in liver transplant recipient

HCV genotype	Recommended regimens	Level of evidence	Alternative regimen IFN eligible and SOF & SMV are not available (Naïve or relapser to PEG-IFN/RBV with fibrosis <3)
1	Sofosbuvir 400 mg/d + simeprevir 150 mg/d ± weight-based ribavirin for 12-24 wks or Sofosbuvir 400 mg/d + weight-based ribavirin for 24 wks	B1	Triple therapy: BOC or TPV + PEG-IFN/ weight-based ribavirin for 36-48 wks. (Careful monitoring drug interactions with IC and toxicity)
2 or 3	Sofosbuvir 400 mg/d + weight-based ribavirin for 12-24 wks	B1	Standard PEG-IFN/weight-based ribavirin for 12-24 wks
4	Sofosbuvir 400 mg/d + simeprevir 150 mg/d ± weight-based ribavirin for 12-24 wks	B1	Standard PEG-IFN/weight-based ribavirin for 12-24 wks
1,3,4,5,6	Sofosbuvir 400 mg/d + daclastavir 60 mg/d ± weight-based ribavirin for 12-24 wks	B1	Standard PEG-IFN/weight-based ribavirin for 12-24 wks

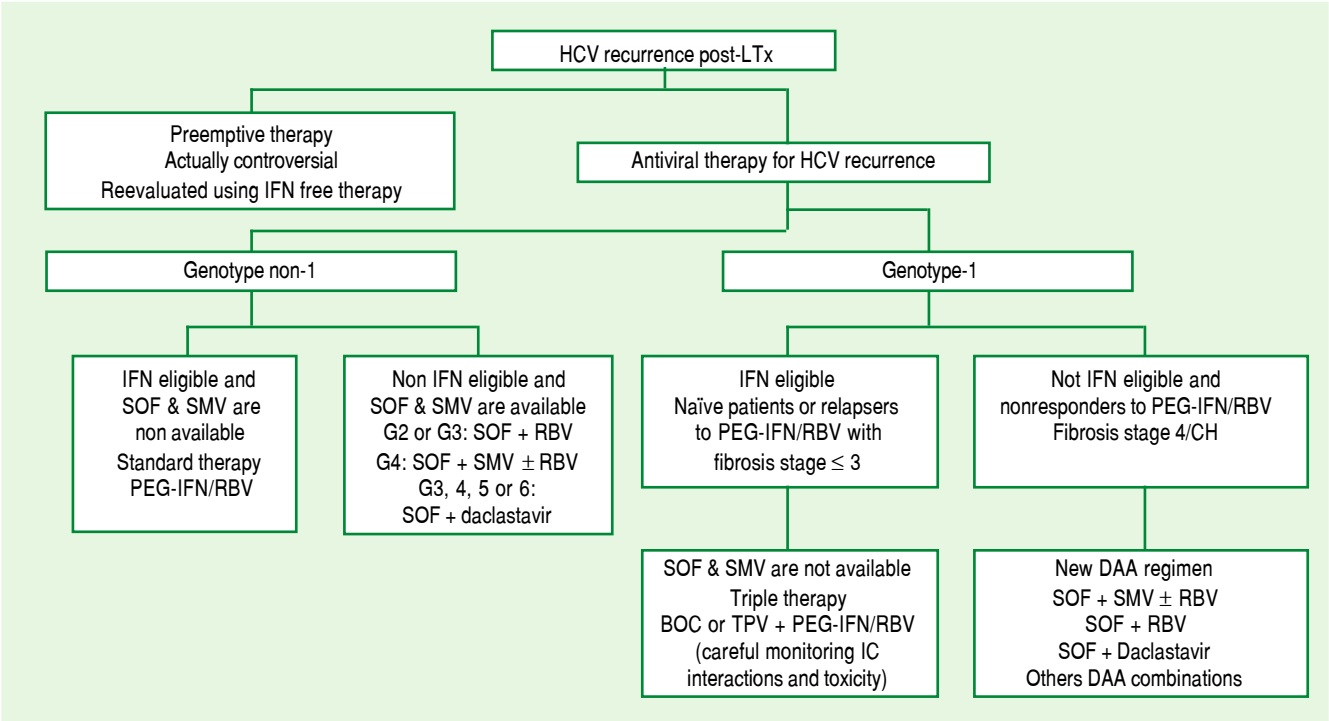

Figure 2. *Proposed algorithm for antiviral HCV strategy after liver transplantation.*

to the hematological toxicity of PEG-IFN/RBV and infections. Although a first-generation PI can be used after LT in GT1 patients, these regimens are associated with serious toxicity and drug-drug interactions, especially with tacrolimus and cyclosporine, which limit their potential benefit. Triple AVT with TVR or BOC was less effective in patients with GT1a, IL-28B polymorphism CT or TT and those who were nonresponders to a previous PEG-IFN/RBV regimen. During triple therapy, the risk of biopsy-proven acute rejection seems to be similar to that in control groups and varies from 4% to 6%.[187-189] In 2014, SOF and SMV are now recommended as part of the preferred or alternative regimens for the treatment of recurrent HCV infection in posttransplant patients. DCVhas also been included in some regimens, depending on HCV GT, but published efficacy data are limited. SMV has not been studied with SOF in the posttransplant setting; however, drug interaction studies in noninfected participants indicate that SMV can be given safely in conjunction with calcineurin inhibitors. The combination of SOFand RBV yielded an SVR rate of 77%, 4 weeks after the end of therapy in 40 patients with posttransplant HCV recurrence.[190] One liver transplant recipient with severe recurrent HCV was reported to have been treated successfully witha combination of SOF and DCV.[191] No clinically significant drug-drug interactions have been reported between SOF, SMV, DCV and calcineurin inhibitors. In Table 7,we have included the recommended and alternative regimens (Figure 2).

RECOMMENDATIONS

A. *The recommended standard of care for liver transplant recipients is treatment of confirmed recurrent liver disease. Significant fibrosis or portal hypertension 1 year after transplantation predicts rapid disease progression and graft loss, and indicates the need for more urgent antiviral treatment* ***(Class B, Level 2)***.

B. *Dose adjustment is not required for tacrolimus or cyclosporine with any of these news AVT combinations. However careful monitoring is important because of the absence of safety data in this population* ***(Class B, Level 1)***.

13. TREATMENT OF SPECIAL POPULATIONS: HCV-HIV COINFECTION

Patients with HIV-HCV coinfection have a faster rate of fibrosis progression, resulting in more frequent occurrences of cirrhosis, end-stage liver disease and HCC.[192,193] Therefore, hepatitis C treatment is an urgent need for this population.

Optimal conditions for treatment are not always possible or similar in all regions of the world, including Latin America. Optimal conditions may involve high-cost medications, maintenance of appropriate facilities, and assurance of adequate numbers and training of staff. Therefore, it is necessary to adapt current recommendations for hepatitis C treatment within the economic capacity of each particular region.[2,67] Taking into account these different aspects, the aim of this section is to discuss the indications for hepatitis C treatment in HIV-HCV coinfected patients in Latin America and to present treatment options for this group of patients.

WHO SHOULD BE TREATED?

In general, indications for HCV treatment in HCV-HIV coinfected people are identical to those in patients with HCV monoinfection.[2,67] Treatment should be prioritized for patients with moderate or significant fibrosis (METAVIR score F2-F4).[67,194-196] In patients with no or mild disease (METAVIR score F0-F1), the indication for, and timing of, therapy can be individualized.

TREATMENT OF HCV

Different drug combinations are available for patients with chronic hepatitis C infection. Indications will depend mainly on the availability of such drugs in different settings.[2]

GT1

Option 1-Treatment with PEG-IFN/RBV

PEG-IFN in combination with RBV is recommended for the treatment of chronic HCV infection rather than standard non-PEG-IFN with RBV.[2,67,194,196]

The published SVR from the five largest controlled studies performed with PEG-IFN/RBV range from 14 to 35 % for GT1 and GT4.[196]

Both PEG-IFN-a molecules can be used. It is recommended that weight-based RBV (1,000 mg/day for < 75kg and 1,200 mg/day for ≥ 75 kg) should be used in coinfected patients. Carriers of HCV GT1 and GT4 with EVR (week 12) but not RVR (week 4) might benefit from extended (72-week) courses of therapy.[196]

Option 2-Treatment with TVR or BOC

People treated with these DAAs had an estimated SVR almost twice that of people receiving only PEG-IFN/RBV. The recommendation for the use of TVR or BOC for HIV-HCV coinfected patients should primarily involve patients with the best chances of SVR and safety. The overall treatment duration of TVR-or BOC-based HCV therapy is 48 weeks.[194] Dosage and futility rules for TVR and BOC should follow their label indications.[197,198]

Dual therapy with PEG-IFN/RBV may be appropriate for selected treatment-naïve patients who may achieve high SVR rates. Treatment-naïve patients with a fibrosis score ≤ F2 and RVR after 4 weeks of treatment with PEG-IFN/RBV may obtain a high rate of SVR, similar to rates obtained with triple therapy including TVR or BOC. This approach could avoid the cost and additional side-effects associated with PI treatment.[67]

Option 3-Treatment with SMV

This combination has been evaluated in coinfected patients in the C212 study. An SVR was achieved in 79% of treatment-naïve patients (42/53), in 87% (13/15) of prior relapsers and in 57% (16/28) of prior null responders.[199] Dosage and futility rules for SMV should follow its label.[200]

Option 4-Treatment with SOF and PEG-IFN/RBV

For HIV-HCV coinfected patients, the SVR rate in a Phase 2 trial was 87 % for GT subtype 1a and 89% (17/19) for subtype 1b (13/15).[201] However, this treatment strategy has not been formally investigated in clinical studies of GT1 IFN-experienced patients. In addition, relatively small numbers of patients with cirrhosis were included.[67]

SOF should be administered with both PEG-IFN-α and RBVfor 12 weeks. The recommended dose of SOF is one 400 mg tablet taken once daily.

Option 5-Treatment with SOF and SMV

This recommendation is based on preliminary results from the COSMOS Phase IIb trial.[202] Patients infected with HCV GT1 can be treated with a combination of daily SOF (400 mg) and daily SMV (150 mg) for 12 weeks.

Option 6-Treatment with SOF and DCV

Both treatment-naïve and treatment-experienced patients infected with HCV GT1 can be treated with a combination of SOF and DCV, including those who failed on a triple combination of PEG-IFN-α, RBV and either TVR or BOC. This recommendation is based on preliminary results from a Phase IIb trial recently published.[19] Patients should be treated with daily SOF (400 mg) and daily DCV (60 mg) for 12 weeks. This combination should be considered especially in patients with predictors of poor response to anti-HCV therapy, prior nonresponders and/or patients with cirrhosis.

GT2

Option 1-Treatment with PEG-IFN and RBV (recommendation B1)[2]

The SVR rate in controlled studies performed with PEG-IFN/RBV ranges from 44 to 73% for GT2 and GT3. Drug doses are the same as for GT1.

Patients with HCV GT2-3 with a RVR-as long as HCV load is low, there is good compliance with treatment, there is not advanced hepatic fibrosis, and weight-based RBV dosing is provided-could benefit from shorter (24 weeks) courses of therapy.[196] For other patients with HCV GT2 or GT3, 48 weeks of therapy could still be advisable.[196]

Option 2-Treatment with SOF and RBV

Patients infected with HCV GT2 should be treated with the combination of SOF and RBV.[67] This recommendation is based on preliminary results from Phase III trials.[67] During the PHOTON 1 trial, SVR24 was 88% for treatment-naïve patients treated for 12 weeks and 92% for treatment-experienced patients treated for 24 weeks.[203] Patients infected with HCV GT2 must be treated with daily weight-based RBV and SOF (400 mg) for 12 weeks.[67]

Therapy should be prolonged to 20 or 24 weeks in patients with cirrhosis, especially if they are treatment experienced *(recommendation B1)*.[67]

Option 3-Treatment with SOF and PEG-IFN/RBV (recommendation B1)[67]

This recommendation is based on preliminary results from Phase II trials.[201] SOF should be administered with both PEG-IGN-α and RBV for 12 weeks. The recommended dose of SOF is 400 mg daily. The dose of RBV should be weight based. This combination could be an alternative for cirrhotic and/or treatment-experienced patients.[67]

GT3

Option 1-Treatment with PEG-IFN/RBV (recommendation B1)[2]

See GT2 treatment with PEG-IFN/RBV.

Option 2-Treatment with SOF, PEG-IFN-α and RBV (recommendation A2)[67]

This recommendation is based on results from Phase II trials.[100,201] Patients infected with HCV GT3 should be treated with a combination of weekly PEG-IFN-α, daily weight-based RBV, and daily SOF (400 mg) for 12 weeks.

Option 3-Treatment with SOF and RBV (recommendation A2)[67]

This recommendation is based on results from Phase III trials.[67,203] Patients infected with HCV GT3 should be treated with daily weight-based RBV and daily SOF(400 mg) for 24 weeks. This therapy is suboptimal in treatment-experienced cirrhotics, for whom an alternative treatment option should be considered.[67]

Option 4-Treatment with SOF and DCV

Patients infected with HCV GT3 could be treated with SOF and DCV.[67] This recommendation is based on preliminary results from a Phase IIb trial recently published,[106] but few data are available with this combination in patients infected with GT3. Patients infected with HCV GT3 should be treated with daily SOF (400 mg) and daily DCV (60 mg) for 12 weeks in treatment-naïve patients or 24 weeks in treatment-experienced patients.[67]

GT4

Option 1-Treatment with PEG-IFN/RBV(recommendation B1)[2]

Drug doses and treatment duration the same as for GT1.

Option 2-Treatment with SOF, PEG-IFN and RBV

Patients infected with HCV GT4 can be treated with weekly PEG-IFN-α, RBV and SOF.[67] Very few data have been presented in HIV-coinfected patients.[201] Drug doses and treatment duration are the same as for GT1.

Other options are also possible, although very few data are available:[67]

1. A combination of weekly PEG-IFN-α, RBV, and SMV;[67]
2. A combination of PEG-IFN-α, RBV and DCV;[67]
3. A combination of RBV and SOF;[67]
4. A combination of SOFand SMV*(recommendation B2)*;[67] or
5. A combination of SOF and DCV.[67]

GT5 AND GT6

Option 1-Treatment with PEG-IFN/RBV

There are no published data regarding the SVR rate for coinfected patients treated with this regimen.[196] Drug doses and treatment duration are the same as for GT1.

Option 2-Treatment with SOF and PEG-IFN/RBV

Patients infected with HCV GT5 or GT6 could be treated with PEG-IFN-α, RBV, and SOF.[67] There are no published data regarding the SVR rate for HIV coinfected patients treated with this regimen. Drug doses and treatment duration are the same as for GT1.

DRUG INTERACTIONS BETWEEN ANTIRETROVIRALS AND DAAS FOR HEPATITIS C TREATMENT

Relevant drug-drug interactions between the DAAs and antiretroviral drugs occur during hepatitis C treatment in HIV coinfected patients. Data on current recommendations regarding the use of antiretroviral drugs during HCV treatment are summarized in table 8.

RECOMMENDATIONS

1. *All treatment-naïve and treatment-experienced patients with compensated disease because of HCV and HIV should be considered for therapy* ***(recommendation A1)***.[67]

2. *Patients with contraindications to use of IFN or patients intolerant to IFN should be considered for IFN-free therapy* ***(recommendation A1)***.[67]

GT1

Option 1-Treatment with PEG-IFN/RBV

PEG-IFN/RBV is recommended for the treatment of chronic HCV infection rather than standard non-PEG-IFN with RBV (recommendation B1).[2,67,194,196]

Option 2-Treatment with TVR or BOC

Treatment with TVR or BOC, given in combination withPEG-IFN-α and RBV, is suggested for GT1 chronic HCV infection, rather than PEG-IFN/RBV alone (recommendation B2).[2,194]

This category includes patients with F2-F3 METAVIR scores. Cirrhotic patients should also be selected, excluding those with platelets < 100,000/mm^3 in combination with serum albumin < 35 mg/dL (recommendation B2).[67,204-207]

Option 3-Treatment with SMV

SMV, given in combination with PEG-IFN-α and RBV, is recommended for people with HCV GT1b infection and for people with HCV GT1a infection without the Q80K polymorphism, rather than PEG-IFN/RBV alone (recommendation A1).[2,67]

Option 4-Treatment with SOF and PEG-IFN/RBV

SOF, given in combination with PEG-IFN-α and RBV, is recommended in GT1 infection rather than

Table 8. Recommendations regarding the use of antiretroviral drugs during hepatitis C treatment.

	Telaprevir[197,208]	Boceprevir[198,208]	Simeprevir[67,200,208]	Sofosbuvir[208,209]	Daclastavir[67,208]
Atazanavir	Monitor for hyperbilirubinaemia	Consider ona case-bycasebasis	Not recommended	Recommended	Recommended at 30 mg/day
Lopinavir	Potential interaction	Not recommended	Not recommended	Recommended	No data
Indinavir	Potential interaction	Potential interaction	Not recommended	Recommended	No data
Fosamprenavir	Potential interaction	Potential interaction	Not recommended	Recommended	No data
Nelfinavir	Potential interaction	Potential interaction	Not recommended	Not recommended	No data
Saquinavir	Potential interaction	Potential interaction	Not recommended		No data
Tipranavir	Potential interaction	Potential interaction	Not recommended	Not recommended	No data
Darunavir	Not recommended	Not recommended	Not recommended	Recommended	No data
Efavirenz	Increase dose to 1,125 mg three times daily	Not recommended	Not recommended	Recommended	Recommended at 90 mg once daily dosing
Rilpivirine	Caution for QT interval prolongation	Recommended	Recommended	Recommended	No data
Etravirine	Recommended	Potential interaction	Not recommended	No data	No data
Delavirdine	Potential interaction	Potential interaction	Not recommended	Recommended	No data
Nevirapine	Potential interaction	Potential interaction	Not recommended	Recommended	No data
Raltegravir	Recommended	Recommended	Recommended	Recommended	No data
Dolutegravir	Recommended	Recommended		Recommended	No data
Maraviroc	Potential interaction	Potential interaction	Recommended	Recommended	No data
Tenofovir	Potential interaction	Recommended	Recommended	Recommended	No data
Abacavir	Potential interaction	Recommended	Recommended	Recommended	No data
Emtricitabine	Recommended	Recommended	Recommended	Recommended	No data
Lamivudine	Recommended	Recommended	Recommended	Recommended	No data
Zidovudine	Potential interaction	Potential interaction	Recommended	Recommended	No data

PEG-IFN/RBV alone or PEG-IFN/RBV and TVR or BOC (recommendation A1).[2,67]

The dose of RBV should be weight based. SOF in combination with daily weight-based RBV for 24 weeks can be considered for patients with HCV GT1 infection who are IFN ineligible (recommendation B2).[67]

Option 5-Treatment with SOF and SMV

This combination should be considered especially in patients with predictors of poor response to anti-HCV therapy, prior nonresponders and/or patients with cirrhosis (recommendation A1).[67]

Option 6-Treatment with SOF and DCV

Both treatment-naïve patients and treatment-experienced patients infected with HCV GT1 can be treated with a combination of SOF and DCV, including those who failed a triple combination of PEG-IFN-α, RBV and either TVR or BOC (recommendation B1).[67] This recommendation is based on preliminary results from a Phase IIb trial recently published.[106] Patients should be treated with daily SOF (400 mg) and daily DCV (60 mg) for 12 weeks. This combination should be considered especially in patients with predictors of poor response to anti-HCV therapy, prior nonresponders and/or patients with cirrhosis (recommendation A1).[67]

GT2

Option 1-Treatment with PEG-IFN/RBV[2]

SVRs from controlled studies performed with PEG-IFN/RBV range from 44 to 73% for GT2 and GT3. Drug doses the same as for GT1 (recommendation B1).[2]

Option 2-Treatment with SOF and RBV

Patients infected with HCV GT2 should be treated with the combination of SOF and RBV (recommendation A1).[67]

This recommendation is based on preliminary results from Phase III trials.[67] During the PHOTON 1 trial, SVR24 was 88% for treatment-naïve patients treated for 12 weeks and 92% for treatment-experienced patients treated for 24 weeks.[203] Patients infected with HCV GT2 must be treated with daily weight-based RBV and SOF (400 mg) for 12 weeks (recommendation A1).[67]

Option 3-Treatment with SOF and PEG-IFN/RBV (recommendation B1)[67]

This recommendation is based on preliminary results from Phase II trials.[201] SOF should be administered with both PEG-IFN-α and RBV for 12 weeks. The recommended dose of SOF is 400 mg daily. The dose of RBV should be weight based (recommendation B1).

GT3

Option 3-Treatment with SOF and RBV (recommendation A2)[67]

This recommendation is based on results from Phase III trials.[67,203] Patients infected with HCV GT3 should be treated with daily weight-based RBV and daily SOF(400 mg) for 24 weeks. This therapy is suboptimal in treatment-experienced cirrhotics, for whom an alternative treatment option should be considered (recommendation A2).

Few data are available with this combination in patients infected with GT3. Patients infected with HCV GT3 should be treated with daily SOF (400 mg) and daily DCV (60 mg) for 12 weeks in treatment-naïve patients or 24 weeks in treatment-experienced patients (recommendation B1).[67]

GT4

Option 2-Treatment with SOF and PEG-IFN/RBV

Patients infected with HCV GT4 can be treated with weekly PEG-IFN-α, RBV and SOF (recommendation B1).[67]

Other options are also possible, although very few data are available.[67]

- *Combination of weekly PEG-IFN-α, ribavirin, and SMV (recommendation B1).*[67]
- *Combination of PEG IFN-α, RBV and DCV (recommendation B1).*[67]
- *Combination of RBV and SOF (recommendation C2).*[67]
- *Combination of SOF and SMV (recommendation B2).*[67]
- *Combination of SOF and DCV (recommendation B2).*[67]

GT5 AND GT6

Option 2-Treatment with SOF and PEG-IFN/RBV

Patients infected with HCV GT5 or GT6 could be treated with PEG-IFN-α, RBV, and SOF (recommendation B1).[67]

14. TREATMENT OF SPECIAL POPULATIONS: HBV COINFECTION

INTRODUCTION

HBV/HCV share the same pathways of viral transmission, and coinfection is frequent in several geographical areas where both infections show a high level of endemicity.[210,211] Very few data have been published on the spread of HBV-HCV coinfection in these areas, although HBV-HCV coinfection is a very frequent finding in those populations associated with a high risk of acquiring both infections, such as injecting drug users,[212] hemodialysis patients[213] and HIV-infected people.[214] It is noteworthy that some people may simultaneously acquire HBV and HCV infection from subjects replicating both HBV and HCV. Despite scanty data in the literature, several case reports showed a pattern of disease where a decreased HBV replication is associated with a clearly documented HCV disease progression.[215,216]

The second pattern is a superinfection of HBV on chronic hepatitis C, or HCV on HBV chronic carriers. Although an inhibitory effect of HBV superinfection on chronic HCV replication has been clearly documented, the clinical course of acute HBV in these patients was described as severe.[217] Despite the association with a more severe clinical course, chronic HBV-HCV coinfection is characterized by a reciprocal inhibition of viral replication;[218] the strong inhibitory effect is exerted by the superinfecting virus on the preexisting one.[219] In a single 1-year longitudinal study, the virological profile of chronic HBV-HCV coinfection was characterized by dynamic fluctuations in HBV and HCV viremia in one-third of cases, whereas in the remaining cases, it remained constant. Despite the virological evidence of viral interference in patients with HBV-HCV coinfection, the interaction between these viruses remains to be fully understood, and further studies using *in vitro* models are needed. No direct reciprocal interference was found in one *in vitro* model, and indirect mechanisms likely to be mediated by innate and/or adaptive host immune responses have been suggested.[220]

The current international guide lines do not suggest first-line treatment for these patients.[65,221] However, recently other international associations using GRADE have suggested PEG-IFN-α, RBV, and PIs following the same rules as in monoinfected patients *(recommendation B2)*.[67] The expert panel also stated that if HBV replication is at significant levels before, during, or after HCV clearance, concurrent HBV nucleoside/nucleotide analogue therapy may be indicated *(recommendation C2)*. Latin American guidelines (ALEH 2011) suggested treating the dominant virus without using a rating system of recommendation levels.[222] It seems rational to hypothesize that effective treatment may eradicate HCV infection and inhibit HBV replication without severe adverse effects. The careful monitoring of disease progression, viral replication, viral suppression, possible predominance of one virus over the other, comorbidities and cofactors (e.g., metabolic syndrome, alcohol or drug intake), presence of hepatitis delta virus (HDV) or HIV infection, host genetic factors and type of response to previous antiviral treatments is warranted, to select the best therapy for patients with HBV-HCV coinfection. Treatment of chronic HBV-HCV may change according to HBV or HCV replication predominance. Different therapy options for these different viral scenarios will be discussed here.

Treatment in HCV RNA-positive/HBV DNA-negative patients

Studies published from the beginning of 2000 onwards showed poor efficacy of standard IFN-α plus RBV for the treatment of patients with chronic HBV-HCV coinfection and HCV replication.[223] However, Liu *et al.*[224] conducted a comparative, multicenter open-label study that showed the efficacy and safety of PEG-IFN-α2a plus RBV in 161 patients with chronic HBV-HCV coinfection, all with active HCV replication, and in 160 control patients with HCV monoinfection. No difference in the rate of HCV SVR was observed between patients with dual infection or monoinfection. Indeed, for HCV GT1, the SVR rate was 72.2% in patients with dual infection and 77.3% in HCV-monoinfected patients, whereas for patients with HCV GT2/3, the SVR rates were 82.8 and 84%, respectively. In a 5-year follow-up study published in 2013, the same group showed the durability of HCV SVR in HBV-HCV coinfected patients treated with PEG-IFN. No data have yet been published on the efficacy of DAAs in combination with PEG-IFN plus RBV or with IFN-free drugs for treating patients with chronic HBV-HCV coinfection. However, taking into account that in HCV GT1 monoinfection, triple therapy achieved SVR more frequently than dual therapy in therapy-naïve, relapser and previous nonresponder patients,[225] it seems that triple therapy may be also

an option for patients with chronic HBV-HCV GT1 coinfection, a hypothesis that awaits confirmation in clinical trials. Whether IFN-free DAA-based therapy will be effective in eradicating HCV infection also in HBV-HCV coinfected patients is a very important issue that warrants investigation.[226] An attempt at a treatment algorithm was proposed by Sagnelli, *et al.*[227]

Treatment in HBV DNA-positive/HCV RNA-negative patients

Information on the use of anti-HBV drugs for patients with chronic HBV-HCV coinfection is scarce, most likely because HBV predominates less frequently than HCV. In the above mentioned study by Liu *et al.*,[224] 145 patients with HBV-HCV coinfection, all HCVRNA-positive and 68 (46.9%) HBVDNA-positive at baseline, were treated with PEG-IFN-α2a plus RBV. At the end of treatment, 55% of the 68 became HBVDNA-negative, and more interestingly, 11.2% of all 145 treated patients became HBV surface antigen (HBsAg)negative. In subsequent analyses, the same researchers described an association between lower HBsAg levels at baseline and a greater likelihood of clearing HBsAg during treatment (40% for HBsAg level < 20 IU/mL *vs.* 2.2% for HBsAg level > 20 IU/mL; $p < 0.05$),[228] and a 30% cumulative HBsAg seroclearance rate at the end of a 5-year posttreatment follow-up. However, after a longer follow-up period of 4 years, the authors showed that HBV DNA became positive in 47 out of 76 cases (61.8%), with this reappearance being transient in 21 (44.7%), intermittent in 12 (25.5%) and sustained in 14 (29.8%).[226]

In line with the above mentioned studies, Yu, *et al.*[229] observed that 11 of 46 (23.9%) patients with HBV-HCV coinfection and negative HBV DNA at baseline became HBVDNA-positive after anti-HCV PEG-IFN plus RBV treatment. The HBV reactivation rate was significantly higher in patients who achieved HCV SVR (33.3%) than in those who failed to achieve this favorable result (8.7%) ($p = 0.036$). An algorithm was also proposed by Sagnelli, *et al.* for treatment of this group of patients.[227]

RECOMMENDATIONS

1. *An exhaustive analysis of the disease progression, virus predominance, comorbidities, presence of hepatitis delta virus or HIV infection, and response to previous antiviral treatments is crucial for a better selection of patients for treatment.*

2. *Only the EASL Clinical Practice Guidelines (CPGs) have recommended HCV/HBV coinfection treatment using the GRADE recommendation system.*

3. *Effective treatment should eradicate HCV infection and inhibit HBV replication. Peg IFN and ribavirin may be useful to treat HCV-RNA-positive/HBV-DNA-negative patients, and Peg IFN and nucleoside/nucleotide analogs (NUC) may be useful to treat HBV-DNA-positive/HCV-RNA-negative patients* ***(Recommendation C2)***.

4. *No data on the efficacy of combining DAAs plus Peg-IFN and ribavirin treatments and interferon free molecules (sofosbuvir, simeprevir) in HBV/HCV chronic coinfection have been published, but in cases with HCV predominance, Peg-IFN plus ribavirin and a first-generation DAA, such as boceprevir or telaprevir, should provide satisfactory sustained response rates, and significantly reduce the risk of liver-related mortality, as well as all-cause mortality* ***(Recommendation C2)***.

15. HEPATITIS C AND RENAL FAILURE WITHOUT HEMODIALYSIS

The impact of chronic HCV infection and the characteristics of the clinical course of the disease in predialysis renal patients are not very well identified.[230-232] There is a large amount of information regarding hepatitis C in hemodialysis patients, but it is not known whether the clinical course and histopathological aspects of patients under hemodialysis can be extrapolated to predialysis patients.[233-236] Additionally, few studies have evaluated specific aspects of hepatitis C treatment in predialysis patients. All these aspects contribute to the weaker evidence for the recommendations for this specific group of patients.

Treatment indication

The decision to treat is fundamentally based on the stage of renal function, the rate of progression of renal dysfunction and the possibility of preemptive renal transplant, more than on the stage of liver disease.

Renal dysfunction in chronic kidney diseases (CKD) is classified in five stages based on glomerular filtration rate (GFR), as follows.

- GFR > 90 (normal function).
- GFR 60-89 mL/min (mild dysfunction).
- GFR 30-59 mL/min (moderate dysfunction).
- GFR 15-29 mL/min (severe dysfunction).
- RGF < 15 mL/min (end-stage renal disease, ESRD).

In this section, we will refer to patients in stages 2, 3 and 4 of renal dysfunction.[237]

For patients with mild or moderate renal dysfunction, it is important to evaluate the rate of progression of renal disease. If renal function is stable, treatment is recommended. If renal function is unstable and the deterioration of renal function is rapid, it is better to wait and treat when the patient is under hemodialysis (*rating 2C*).

Type of treatment

The treatment of choice is still the combination of IFN-α2a and RBV, depending on the HCVGT.[238] IFN-α2a seems to be the preferred option because PEG-IFN-α2a is cleared by the liver and PEG-IFN-α2b via the kidneys. The recommended dose of PEG-IFN-α2a is 135 mg/week. RBV should be used with caution, and the dose should be adjusted according to creatinine clearance (Table 10). Impaired excretion of RBV occurs in patients with CKD, as RBV is mostly eliminated by the kidney. The accumulation of the drug can exacerbate the anemia in this population already at risk.[238]

The use of erythropoietin is important for maintaining adequate levels of RBV and should be optimized before starting the treatment. Patients should be followed up with weekly blood cell counts during the first month and every 2 weeks thereafter (*rating 2B*).

Information is scarce regarding the use of triple therapy with the first wave of PIsTVR and BOC. Small series show that their use is safe with close monitoring of anemia and renal function. Neither drug requires dose adjustments[239-241] (*rating 1C*).

When using SOF to treat or re-treat HCV infection in patients with appropriate GT, no dosage adjustment is required for patients with mild to moderate renal impairment (GFR > 30 mL/min) (*rating 2B*).[242]

For SMV, no dosage adjustment is required for patients with mild, moderate or severe renal impairment, because renal clearance plays an insignificant role (< 1%) (*rating 2B*).[242]

Table 9. Dose adjustment of PEG-interferon-a and ribavirin for patients with renal dysfunction.

Renal dysfunction	CrCl	Peg-IFN	RBV
Mild 60-89 mL/min	2a- 180 μg/w	Standard dose 2b- 1.5 μg/w	
Moderate	30-59 mL/min	2a- 135 μg/w	200-400 mg 3 x s/week
		2b-1 μg/w	
Severe	< 30 mL/min	2a-135 μg/w 2b-1 μg/w	200 mg/day

16. RENAL FAILURE WITH HEMODIALYSIS AND INDICATION FOR KIDNEY TRANSPLANTATION

Epidemiology

It has been shown that the prevalence of HCV infection is invariably greater in patients on hemodialysis than in the general population but with very important variations in the incidence and prevalence in different geographical areas. Using third-generation anti-HCV antibody tests, the reported prevalence of HCV infection in hemodialysis patients varies from 5-10% in the USA[243] to 49% in Syria.[244]

HCV infection has been found in 5-40% of patients after a kidney transplant, with a mean prevalence of 6.8%.[245]

In Brazil, the HCV infection prevalence varies from 4 to 14%, with a predominance of GT1.[246] It has been reported to be 6.4% in Mexico[247], 6.1% in Colombia[248] and 25%-75% in Venezuela.[249] The anti-HCV antibody prevalence in kidney transplant recipients was 20.6% in a report from Argentina,[250] with no impact on mortality or morbidity.

HCV infection affectsthe survival of patients on hemodialysis. A meta-analysis including more than 2,000 patients showed an increased relative risk of mortality in infected patients of 1.57 (95% CI: 1.33-1.86) compared with uninfected patients.[251] Even though infection by HCV has been shown also to have a negative impact on post-kidney-transplant survival,[252,253] life expectancy is better in infected patients undergoing a transplant than in those not transplanted.[254]

Diagnosis and evaluation

Diagnosis of HCV infection in patients on hemodialysis and after a renal transplant relies primarily on antibodies (third-generation ELISA). HCV viremia has been reported in anti-HCV antibody-negative patients (occult HCV infection), but this seems to be a more important phenomenon in high-prevalence areas and in patients with unexplained abnormal aminotransferase levels. HCV RNA tests, either qualitative PCR or quantitative assays, are considered to be the most sensitive diagnostic methods, but there are several reasons that may explain false positive and false negative results.[255]

HCV infection in hemodialysis patients is generally asymptomatic. There is no good correlation between aminotransferase levels and viral load or liver biopsy findings.[236] Therefore, a liver biopsy has been suggested as the only reliable method for evaluating the severity of liver fibrosis.[256] More recently, noninvasive methods for evaluating liver fibrosis such as transient elastography (Fibroscan®) have been shown to be reliable in the post-kidney-transplantation setting[257] and will probably be preferred to liver biopsy in patients with renal dysfunction, who may have a higher risk of complications after a liver biopsy.

Treatment

Given that conventional IFN-based treatments have low efficacy and low tolerance in patients on maintenance hemodialysis, it is generally recommended that therapy should be offered to patients who are at the highest risk of complications due to the infection, such as those with compensated cirrhosis or advanced fibrosis and those considered for a renal transplant.[257-263] This means that evaluation of liver fibrosis in these patients is paramount for decision making. This indication is very likely to change when IFN-free therapies become the mainstay therapy for HCV infection. Patients with cirrhosis should be evaluated for double liver-kidney transplantation.

IFN and PEG-IFN

In a retrospective meta-analysis, regular IFN has been shown to be associated with a 41% and PEG-IFN with a 37% chance of SVR.[264] Regular IFN-α2b at a dose of 3 million units 3 times per week for 6-12 months is usually recommended.[256] The half-life of PEG-IFN is markedly increased in patients with ESRD: a recent study showed that PEG-IFN-α2a (135 μg/week) plus low-dose RBV (200 mg/day) for 48 weeks had a better SVR than monotherapy (64 *vs.* 33%) but with more side effects.[238]

RBV

RBV clearance is markedly reduced in renal insufficiency and RBV,and its metabolites are not removed by hemodialysis.[265] Thus, RBVuse in patients with creatinine clearance below 50 mL/min is not generally recommended, and if indicated, a low dose should be used (200 mg/day) with very close follow-up of hemoglobin level and titration of erythropoietin dose to treat anemia.

BOC and TVR

There are few data about the use of the first-generation PIsBOC and TVR in ESRD. Both BOC and TVR are metabolized primarily by the liver to inactive metabolites, so theoretically, no dosage adjustments are necessary in patients with ESRD on dialysis. A small case report shows promising results of TVR use in four patients undergoing hemodialysis.[266]

SOF and SMV

SOF, a nucleotide analog HCV polymerase inhibitor, is metabolized in the liver to its active form (GS-461203), and its inactive metabolites are eliminated by the kidney by glomerular filtration and active tubular secretion. No dose modification is required for mild to moderate renal insufficiency, but its safety has not been established in patients with severe renal impairment or ESRD. There are studies being currently conducted of SOF in this patient population.

SMV is a second-generation PIthat is almost exclusively metabolized in the liver by CYP3A4. Renal elimination of SMV and its metabolites is negligible, but to date, there is insufficient information for treatment in patients with creatinine clearance below 30 mL/min or on maintenance dialysis.

Prevention

Fortunately, HCV infection in hemodialysis patients seems to be declining. Several risk factors have been associated with an increased risk of infection, including the number of blood transfusions,[267] the duration of renal insufficiency,[268] the mode of dialysis (greater in hemodialysis than in peritoneal dialysis)[269] and strikingly, the prevalence of HCV infection in the dialysis unit.[270,271] The available information shows that nosocomial transmission is the most common method of spread of the virus. Needlestick injury,[272] physical proximity to an infected patient[271] and using the same dialysis machine[273] have been linked to an increased risk of HCV transmission, but there is good evidence that breakdown in standard infection-control practices (e.g., failure to change gloves or using multi-dose heparin vials) is the most common route of HCV transmission in outbreaks.[274-276] All this evidence suggests that the best way of preventing HCV infection in dialysis units is the strict enforcement of universal precautions,[277] with the use of dedicated dialysis machines for HCV-infected patients being more controversial and not mandatory.

RECOMMENDATIONS

1. *In patients with ESRD and on dialysis, advanced liver fibrosis and candidacy for kidney transplantation are strong indications for antiviral treatment* ***(Class 1, Level B)***.
2. *Patients on dialysis should be treated with regular IFN (3 MU 3 times per week) and low-dose RBV for 48 weeks* ***(Class 1, Level C)***.
3. *PEG-IFN-α2a at an adjusted dose can also be used* ***(Class 2, Level A)***.
4. *TVR or BOC could be added with caution to treatment of GT1 patients* ***(Class 2, Level C)***.
5. *Strict adherence to universal precautions of infection control is the main action required in hemodialysis units to prevent transmission of HCV infection* ***(Class 1, Level B)***.
6. *Patients with ESRD should be tested with a sensitive antibody assay for anti-HCV antibodies and infection confirmed by a sensitive HCV RNA test* ***(Class 1, Level A)***.
7. *Patients with ESRD and unexplained abnormal aminotransferase levels should be tested for HCV RNA even in the absence of detectable anti-HCV antibodies* ***(Class 2, Level C)***.

17. DRUG-DRUG INTERACTIONS OF DAAs

The advent of TVRand BOC has meant that knowledge of drug–drug interactions, a common and important aspect in the evaluation of patients starting and continuing on HCV therapy, has increased.

Drug-drug interactions are a difficult issue because only a relatively small number of drug–drug interaction studies can ever be performed during the drug development process, and subsequent postlicensing testing is an important method of detecting these.

BOC is given at 800 mg every 8 h with food. The area under the plasma concentration time curve (AUC) is increased up to 65% with food, although the bioavailability is similar whether taken with a high-fat or low-fat meal.[278] BOC is metabolized by aldo-keto reductases (AKR1C2, AKR1C3) and CYP3A4.[279] BOC is also a substrate for the efflux transporter P-glycoprotein (P-gp), which is present in many tissues, including the gastrointestinal tract, liver, blood-brain barrier and placenta.

TVR is given at 750 mg every 8 h. However, twice-daily dosing with 1,125 mg demonstrates an equivalent SVR to thrice-daily dosing.[280,281] TVR needs to be taken with a high-fat (> 20 g) meal/snack to give optional systemic availability.[282] The primary route of metabolism of TVR is CYP3A4, and like many CYP3A4 substrates, it is also transported by P-gp.[283]

Both agents appear to be mechanism-based inhibitors of CYP3A; in addition to the inhibitory effect on CYP3A, both BOC and TVR are inhibitors of P-gp. TVR did not inhibit CYP1A2, CYP2C9, CYP2C19 or CYP2D6 and has a low potential to induce CYP2C, CYP3A or CYP1A.[284] Similarly, BOC did not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP2E1, and there was no evidence of induction of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP2D6.[278,285] Despite these clear effects, there are differences between the European[278,286] supplementary protection certificate (SPC) and the USA prescribing information regarding the cautions about drug-drug interactions.

The area of prolongation of the QT interval on electrocardiogram is an important issue when a patient is using BOC or TVR. TVR should not be coadministered with a Class Ia or III antiarrhythmic and should be used with caution with Class Ic antiarrhythmic drugs that are known to induce QT prolongation and that are CYP3A substrates, and drugs known to prolong the QT interval for which the metabolism is not mainly CYP3A dependent.[286] BOC should not be coadministered with drugs that are dependent on CYP3A4 for clearance; this includes drugs such as pimozide, lumefantrine, and sunitinib, which have a tendency to prolong QT. Perhaps the most pragmatic approach is to identify those drugs that should be avoided when BOC or TVR is used (Table 10).

In the era of DAA agents, health care providers involved in the treatment of patients with HCV must consider potential drug interactions between DAAs and other drugs and supplements. Table 12 provides an algorithm for screening, adjusting and monitoring of potential drug interactions with DAA agents.[287] Some specific and common examples of drug-drug interactions are given. The increase in cyclosporine levels is 2.7-fold with BOC[287] and 4.6-fold with TVR.[288] Similarly, for tacrolimus, the in-

Table 10. Co-medications contraindicated with boceprevir (BOC) and telaprevir (TVR).

Medication	Interaction	
	BOC	TVR
Amiodarone	No	Yes
Bepridil	Yes	Yes
Quinidine	No	Yes
Rifampicin	Yes	Yes
Carbamazepine	Yes	Yes
Phenobarbital	Yes	Yes
Phenytoin	Yes	Yes
Dihydroergotamine	Yes	Yes
Ergotamine	Yes	Yes
Methylergonovine	Yes	Yes
Imatinib	Yes	Yes
Sunitinib	Yes	Yes
Halofantrine	Yes	Yes
Lumefantrine	Yes	Yes
Pimozide	Yes	Yes
Midazolam (oral)	Yes	Yes
Triazolam	Yes	Yes
Sotalol	No	Yes
Drospirenone	Yes	No
Cisapride	Yes	Yes
St John's Wort	Yes	Yes
Sildenafil (pulmonary arterial hypertension)	Yes	Yes
Tadalafil (pulmonary arterial hypertension)	Yes	Yes
Atorvastatin	No	Yes
Lovastatin	Yes	Yes
Simvastatin	Yes	Yes
Alfuzosin	Yes	Yes
Ergonovine	Yes	Yes

Adapted: Back D. 2013.

Table 11. Drug-drug interactions with newer antivirals.

Agent	Profile	Interactions reported
• ***Protease inhibitors***		
Faldaprevir	Moderate inhibitor of CYP3A.	Midazolam, omeprazole, wafarin, efavirenz, caffeine, dextromethorphan.
Simeprevir	Weak inhibitor of CYP3A and P-gp.	Methadone, midazolam, escitalopram, rilpivirine, raltegravir, tenofovir, cyclosporine, tacrolimus, ethinylestradiol/norethisterone, efavirenz.
Asunaprevir	Weak inhibitor of CYP2D6 and P-gp. Weakinducer of CYP3A4.	Midazolam, losartan, omeprazole, caffeine, dextromethorphan.
Danoprevir	CYP3A substrate.	Methadone, omeprazole, ranitidine, warfarin.
• ***Non-nucleoside polymerase inhibitors***		
Filibuvir	Weak inducer and inhibitor of CYP3A.	Midazolam, ketoconazole.
• ***NS5A inhibitors***		
Daclatasvir	P-gp inhibitor	Tenofovir, efavirenz, atazanavir, ethinlyoestradiol/norgestimate.
• ***Nucleoside polymerase inhibitors***		
Sofosbuvir	Not a CYP3A substrate.	
Renally excreted	Methadone, efavirenz, rilpivirine, raltegravir, tenofovir, emtricitabine, darunavir, cyclosporine, tacrolimus.	

Adapted: Back D. 2013.

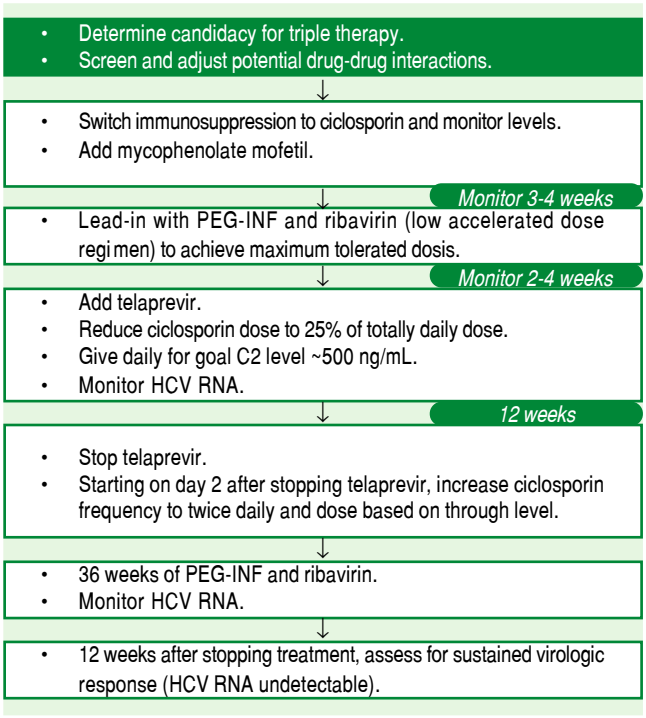

Figure 3. *Algorithm to manage post-transplant patient and drug-drug interactions.* **Adapted**: *Back D. 2013.*

crease is 17-fold with BOC and 70-fold with TVR. Atorvastatin has a 7.9-fold increase in exposure with TVR and 2.3-fold with BOC.[289-291] This suggests that during treatment with DAAs, statin treatment could be stopped temporarily.

Antiviral treatments for HIV are also an important concern: both BOC and TVR have bidirectional interactions with ritonavir-boosted HIV PIs, the magnitude and direction of which has been of concern in relation to antiviral efficacy. For TVR, darunavir/ritonavir, lopinavir/ritonavir and fosamprenavir/ritonavir are not recommended.[286] For BOC, darunavir/ritonavir, atazanavir/ritonavir and lopinavir/ritonavir are not recommended.

Although TVR and BOC do not currently have regulatory approval for posttransplant patients, these individuals are arguably the patients in greatest need of treatment. For this reason, the protocol from the University of Colorado Denver, USA for using triple therapy in patients with recurrent HCV after LT could be considered (Figure 4).[283]

The available information for the most recent antivirals is limited and will be continuously updated.

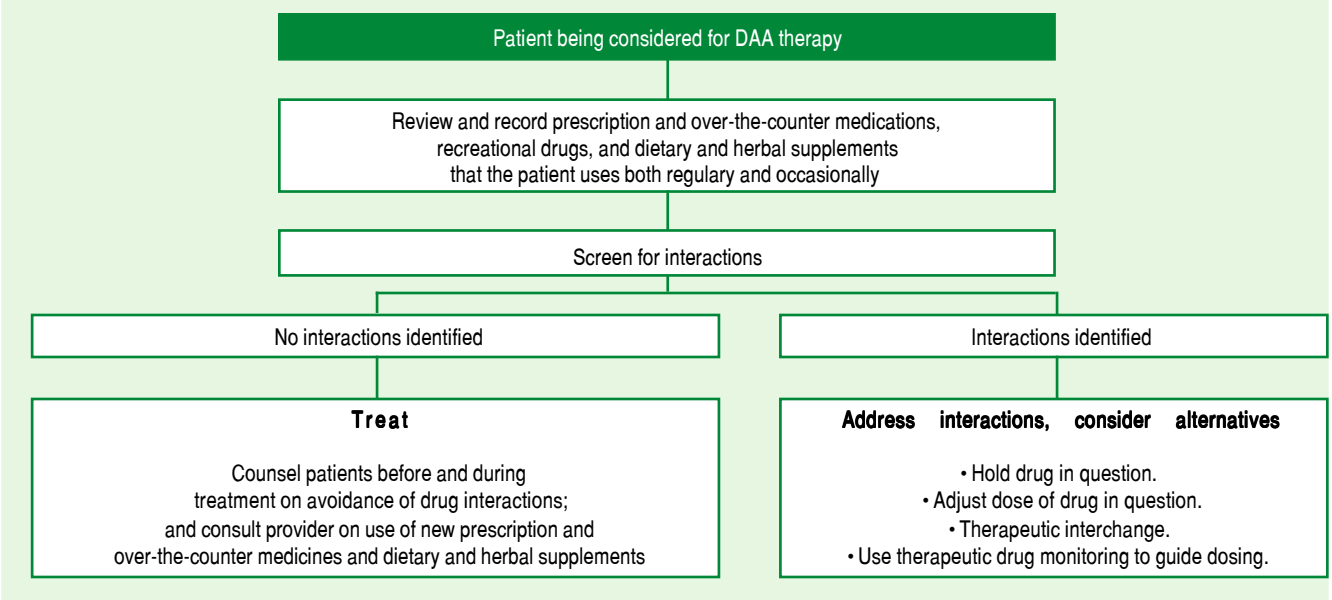

***Figure 4**. Algorithm to search and identify drug-drug interactions.* Adapted: *Back D. 2013.*

However, despite the lack of availability, some information has been published[286] suggesting several interactions with many commonly used drugs including anticoagulants, benzodiazepines and other antivirals (Table 11).

In conclusion, the study of drug-drug interactions is a very active field for gastroenterologists and hepatologists, and technology will help us to offer the best outcomes with fewer adverse events in patients treated with multiple drugs (Figures 3 and 4).

RECOMMENDATIONS

All patients under treatment with direct acting antivirals should be screened sistematically for drug interactions, including herbal or over the counter drugs ***(Class 1, Level C)***.

18. TREATMENT OF SPECIAL POPULATIONS: TREATMENT OF PATIENTS WITH EXTRAHEPATIC MANIFESTATIONS (CRYOGLOBULINEMIA, LICHEN, OVERLAP SYNDROMES, PCT)

HCV is at the same time a hepatotropic and a lymphotropic virus and may cause hepatic and extrahepatic disease. Epidemiological data and biological plausibility support this association.[292,293] The disappearance of these manifestations after viral clearance is a confirmation of the pathogenic role played by HCV in these situations.[294,295] Associations between HCV infection and other clinical conditions, including dermatological, neurological, digestive, endocrinologic and pulmonary disorders, have been described previously.[292,294,296–298]

Among the numerous cutaneous manifestations, the most important are mixed cryoglobulinemia (MC), porphyria cutaneatarda (PCT) and lichen planus.[292–294,296] PCT is characterized by deficient activity of the heme synthetic enzyme uroporphyrinogen decarboxylase. The main cutaneous manifestation is the presence of blisters in areas of sun exposure that lead to milia, dyspigmentation and scarring. HCV infection favors the clinical expression of the disease, and in many cases clearance of the virus will lead to disappearance of the manifestations of PCT. Thus, the best treatment will be the best antiviral drug available in each country.[292,296,299] The initial management of PCT consists of phlebotomy to produce iron deficiency, and avoidance of sunlight, alcohol, estrogen and other chemicals/substances that can precipitate the disorder.

Lichen planus is an inflammatory pruritic disease of the skin and mucous membranes characterized by distinctive papules, with a predilection for the flexor surfaces and trunk. It can be associated with some commonly used drugs such as nonsteroidal anti-inflammatory drugs and hydrochlorothiazide, and in some geographic areas, it is associated with HCV with a higher incidence than the uninfected population. IFN treatment can exacerbate previous lichen lesions and in some cases can trigger the disease.[296,300] It is a skin disease with exacerbations and remissions, and there are no reports of the outcome of the disease after elimination of HCV infection with an antiviral treatment. Therefore, careful consideration is required before starting IFN-based treatment, and these patients should await IFN-free treatment if possible (*weak recommendation*).[301]

Overlap syndrome is the occurrence of autoimmune hepatitis in patients with HCV infection. It is a rare association, and the diagnosis is made with a combination of clinical, laboratory and histological features. It is very important for it to be evaluated-correctly before treatment because IFN can exacerbate the autoimmune disease. Very high aminotransferase levels in association with hypergammaglobulinemia and high titers of autoantibodies raise the suspicion of overlap disease that should be confirmed with histological assessment. Liver biopsy should reveal inflammation (piecemeal and acinar necrosis), with predominant presence of plasmocytes and/or confluent necrosis,which is an uncommon feature of hepatitis C infection.

The treatment in these typical cases of overlap should be initiated with immunosuppressive drugs, because in some cases, the disease is severe with rapid evolution to cirrhosis and hepatic failure (*weak recommendation*). However, we know that autoimmune hepatitis can be often be triggered by a viral infection. With the advent of DAAs and IFN-free treatments that cause a rapid decline in viral load and a high rate of disappearance of hepatitis C infection, an attempt to eradicate this infection could be the first step, with the use of immunosuppressive treatment saved for those cases with permanent liver injury.[302]

The chronic antigenic stimulation of the humoral immune system in patients with chronic hepatitis C leads to an increase in titers of monoclonal and polyclonal antibodies.[303] It has been postulated that a complex of anti-HCV-HCV lipoprotein could act as a B cell superantigen leading to the synthesis of non-HCV-reactive IgM with rheumatoid factor-like activity. These autoantibodies produce immune complexes that circulate in the body and are deposited in small-to-medium blood vessels, resulting in complement activation and extrahepatic injury.

The most common manifestation of MC is an asymptomatic cryoglobulin in the serum that can be shown in 20-40% of infected patients, but only 3-5% of HCV chronic hepatitis patients have symptomatic disease (cryoglobulinemic vasculitis). There are many organs that could be involved, but the most common clinical presentations are skin (leukoclastic vasculitis) followed by joint, neurological, renal and digestive involvement. In most cases (80%), the disease is mild or moderate and is characterized by recurrent vasculitis (purpura) in the legs and arthralgias, but severe disease with membranoproliferative glomerulonephritis, cutaneous involvement with ulcers and ischemic neurosis, peripheral

or central neuropathy, and mesenteric disease can lead to potentially severe complication and even death.[292,303,304]

The two possible treatments consist of the use of immunosuppressive drugs or antiviral drugs. After the discovery of HCV as the etiologic agent for most cases of MC, a new concern has risen about the use of a high dose of immunosuppressive drugs such as corticosteroids. Antiviral drugs such as PEG-IFN and RBV are the main options in HCV therapy and should be the first step/option in patients with mild or moderate MC. Although most of the reported results have come from case series, a meta-analysis of 10 clinical studies[305] including 300 patients showed clinical improvement in 63% of cases and an SVR of 42%. The problem with this study is its heterogeneity. Patients with different GTsand different grades of liver fibrosis and severity of vasculitis were included. PEG-IFN was prescribed in only 66% of cases, and the number of included cases varied from 9 to 86. However, as could be expected, a small controlled study including 72 MC patients[306] showed better results with PEG-IFN/RBV than with IFN/RBV. The rates of clinical remission and virological response were 67%/56.2% and 62.5%/53%, respectively.

So far, there has been no original study evaluating the new triple therapy for GT1 (PEG-IFN/RBV and NS3 PIssuch as TVR or BOC). Only one study[307] reported partial results after 24 weeks of therapy with this combination in 23 patients with MC. Thirteen patients (56.5%) showed a complete clinical response, and 10 (43.5%) had a partial response. At week 24, 70% of the patients were negative for HCV. It is possible that the final result could be better than conventional therapy for patients with GT1.

An interesting new therapy in MC patients is the use of rituximab (RTX) (anti-CD20), which targets B-cells that are responsible for production of the cryoglobulin, immune complex deposition and finally vasculitis. The main indication for RTX therapy is the absence of response to previous therapies. It is the first-choice therapy for cases of severe vasculitis, which can be followed by IFN-based therapy. Most patients received consecutive 4-weekly IV infusions of 375 mg/m^2 of RTX. The isolated use of RTX[308] caused a rapid and complete clinical response in 73% patients with cutaneous involvement, 70% with glomerulonephritis and 36% with neuropathy. Relapse occurred in 36% of cases, pointing to the need for associated AVT.

There is an ongoing study that evaluates a lower dosage of RTX (250 mg/m^2) and its association with clinical response.[309] This drug is considered to be safe for HCV patients, and even those with liver cirrhosis had similar clinical results.[310]

Based on the limitations of each therapy, a combination of RTX with PEG-IFN/RBV seems plausible. Two recent controlled studies[311,312] compared the efficacy and safety profile of PEG-IFN/RBV versus RTX with PEG-IFN/RBV therapy. In both studies, RTX with PEG-IFN/RBV-treated patients had a shorter time to clinical remission, better renal response rates and higher rates of cryoglobulin clearance. Some relapses occurred after the end of treatment, so it is very important to eradicate the viral infection.

Therapeutic guidelines for these situations are not considered in the international associations guidelines, but at the 16th International Vasculitis & ANCA Workshop,[313] the following recommendations were made.

- Aggressive optimal therapy with PEG-IFN/RBV (plus PIs if HCV GT1 infection) should be considered to be the best treatment for HCV–MC patients with mild to moderate disease. Current treatment duration is 48 weeks for all HCV GTs (*strong recommendation*).[307,313]
- In patients presenting with more severe disease (worsening of renal function, mononeuritis multiplex, extensive skin disease with ulcers and distal necrosis), an induction phase of immunosuppression is often necessary while awaiting the generally slow response to antiviral treatment. RTX is the preferred drug for inducing an initial clinical response, followed by the best available antiviral treatment in each country. This drug combination is very important because it may attack both the B cell arm of autoimmunity and the viral trigger (*strong recommendation*).[313,314]
- For patients presenting with the fulminant form of vasculitis with any of the following events (peripheral necrosis of extremities, central nervous system vasculitis, mesenteric involvement, pulmonary complications, hyperviscosity), apheresis can have immediate results and should be combined with an immunosuppressive drug such as RTX to avoid rebound of MC. Antiviral treatment should be started after clinical improvement of the life-threatening complication.[314]

The prognosis of patients with HCV-positive MC is related to severity of fibrosis, serious infection, central nervous system vasculitis, renal function and/or cardiac involvement.[315]

RECOMMENDATIONS

1. *The initial management of PCT consists of phlebotomy to produce iron deficiency, and avoidance of sunlight, alcohol, estrogen and other chemicals/substances that can precipitate the disorder.*
2. *IFN treatment can exacerbate previous lichen lesions and in some cases can trigger the disease.*

Weak recommendations

1. *Careful consideration should be taken before starting IFN-based treatment, and patients should await IFN-free treatment if possible.*
2. *The treatment in these typical cases of overlap should be initiated with immunosuppressive drugs, because in some cases, the disease is severe with rapid evolution to cirrhosis and hepatic failure.*
   Therapeutic guidelines for these situations are not considered in the international associations' guidelines, but in the 16th International Vasculitis & ANCA Workshop,[313] the following recommendations were made.

1. *Aggressive optimal therapy with PEG-IFN and RBV (plus PIs for HCV GT1 infection) should be considered to be the best treatment for HCV–MC patients with mild to moderate disease. Current treatment duration is 48 weeks for all HCV GTs (strong recommendation).[307,313]*
2. *In patients presenting with more severe disease (worsening of renal function, mononeuritis multiplex, extensive skin disease with ulcers and distal necrosis), an induction phase of immunosuppression is often necessary while awaiting the generally slow response to antiviral treatment. RTX is the preferred drug for inducing an initial clinical response, followed by the best available antiviral treatment in each country. This combination is very important because it may attack both the B cell arm of autoimmunity and the viral trigger (strong recommendation).[313,314]*
3. *For patients presenting with the fulminant form of vasculitis with any of the following events (peripheral necrosis of extremities, central nervous system vasculitis, mesenteric involvement, pulmonary complications, hyperviscosity), apheresis can have immediate results and should be combined with an immunosuppressive drug such as RTX to avoid rebound of MC. Antiviral treatment should be started after clinical improvement of the life-threatening complication.[314]*

19. ABBREVIATIONS

- **AASLD**: American Association for the Study of Liver Diseases.
- **APRI**: AST-to-platelet ratio index.
- **AVT**: antiviral therapy.
- **BOC**: boceprevir.
- **CH**: cholestatic hepatitis.
- **CUPIC**: Compassionate Use of Protease Inhibitors in Viral C Cirrhosis.
- **DAAs**: direct-acting antiviral.
- **DCV**: daclatasvir.
- **EASL**: European Association for the Study of the Liver.
- **ESRD**: end stage of renal disease.
- **GRADE**: Grading of Recommendations Assessment, Development and Evaluation.
- **GT**: genotype.
- **HBV**: hepatitis B virus.
- **HCC**: hepatocellular carcinoma.
- **HCV**: hepatitis C virus.
- **HIV**: human immunodeficiency virus.
- **IFN**: interferon.
- **IVDU**: intravenous drug use.
- **LAASD**: Latin American Association for the Study of the Liver.
- **LT**: liver transplantation.
- **LDV**: ledipasvir.
- **NS**: nonstructural.
- **PCR**: polymerase chain reaction.
- **PCT**: porphyria cutanea tarda.
- **PEG-IFN**: pegylated interferon.
- **PEG-RBV**: pegylated ribavirin.
- **PI**: protease inhibitor.
- **PK**: drug pharmacokinetics.
- **RAV**: resistance-associated viral strain.
- **RBV**: ribavirin.
- **RGT**: response-guided therapy.
- **RNA**: ribonucleic acid.
- **RVR**: rapid virological response.
- **SAE**: serious adverse event.
- **SMV**: simeprevir.
- **SOF**: sofosbuvir.
- **SVR**: sustained virological response.
- **SWE**: shearwave elastography.
- **TVR**: telaprevir.
- **WHO**: World Health Organization.

20. CONFLICT OF INTEREST

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21. REFERENCES

1. Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. *Hepatology* 2013; 57: 1333-42.
2. WHO. Guidelines for the screening, care and treatment of persons with hepatitis C infection. April 2014, accessed by http://www.who.int/hiv/pub/hepatitis/hepatitis-c-guidelines/en/
3. Ly KN, Xing J, Klevens RM, Jiles RB, Ward JW, Holmberg SD. The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. *Ann Intern Med* 2012; 156: 271-8.
4. Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002; 347: 975-982.
5. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, Goodman ZD, 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.
6. Andriulli A, Mangia A, Iacobellis A, Ippolito A, Leandro G, Zeuzem S. Metaanalysis: the outcome of anti-viral therapy in HCV genotype 2 and genotype 3 infected patients with chronic hepatitis. *Aliment Pharmacol Ther* 2008; 28: 397-404.
7. Poordad F, McCone J Jr, Bacon BR, Bruno S, Manns MP, Sulkowski MS, Jacobson IM, et al. SPRINT-2 investigators. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med* 2011; 364: 1195-1206.
8. Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, Marcellin P, et al. ADVANCE Study Team. Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med* 2011; 364: 2405-16.
9. Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, Poordad F, et al. HCV RESPOND-2 Investigators. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med* 2011; 364: 1207-17.
10. Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, Focaccia R, et al. REALIZE Study Team. Telaprevir for retreatment of HCV infection. *N Engl J Med* 2011; 364: 2417-28.
11. Chávez-Tapia NC, Ridruejo E, Alves de Mattos A, Bessone F, Daruich J, Sánchez-Ávila JF, Cheinquer H, et al. Latin American Association for the Study of the Liver. *Ann Hepatol* 2013; 12 (Suppl 2): s3-35.
12. Halfon P, Locarnini S. Hepatitis C virus resistance to protease inhibitors. *J Hepatol* 2011; 55: 192-206.
13. Berger KL, Triki I, Cartier M, Marquis M, Massariol MJ, Böcher WO, Datsenko Y, et al. Baseline hepatitis C virus (HCV) NS3 polymorphisms and their impact on treatment response in clinical studies of the HCV NS3 protease inhibitor faldaprevir. *Antimicrob Agents Chemother* 2014; 58:698-705.
14. Fried MW, Buti M, Dore GJ, Flisiak R, Ferenci P, Jacobson I, Marcellin P, et al. Once-daily simeprevir (TMC435) with pegylated interferon and ribavirin in treatment naïve genotype 1 hepatitis C: the randomized PILLAR study. *Hepatology* 2013; 58: 1918-29.
15. Wang C, Huang H, Valera L, Sun JH, O'Boyle DR 2nd, Nower PT, Jia L, et al. Hepatitis C virus RNA elimination and development of resistance in replicon cells treated with BMS-790052. *Antimicrob Agents Chemother* 2012; 56: 1350-8.
16. Lam AM, Espiritu C, Bansal S, Micolochick Steuer HM, Niu C, Zennou V, Keilman M, et al. Genotype and subtype profiling of PSI-7977 as a nucleotide inhibitor of hepatitis C virus. *Antimicrob Agents Chemother* 2012; 56: 3359-68.
17. Viral Hepatitis Global Policy. World Hepatitis Alliance; 2010.
18. Gidding HF, Amin J, Dore GJ, Ward K, Law MG. Hospital-related morbidity in people notified with hepatitis C: a population-based record linkage study in New South Wales, Australia. *J Hepatol* 2010; 53: 43-9.
19. Duberg AS, Pettersson H, Aleman S, Blaxhult A, Daviðsdóttir L, Hultcrantz R, Bäck E, et al. The burden of hepatitis C in Sweden: a national study of inpatient care. *J Viral Hepatol* 2011; 18: 106-18.
20. Myers RP, Liu M, Shaheen AAM. The burden of hepatitis C virus infection is growing: A Canadian population-based study of hospitalizations from 1994 to 2004. *Can J Gastroenterol* 2008; 22: 381-87.
21. Lavanchy D. The global burden of hepatitis C. *Liver Int* 2009; 29(Suppl 1): S74-81.
22. Lauer GM, Walker BD. Hepatitis C Virus Infection. *N Engl J Med* 2001; 345: 41-52.
23. Younossi ZM, Kanwal F, Saab S, et al. The impact of hepatitis C burden: an evidence-based approach. *Aliment Pharmacol Ther* 2014; 39: 518-31.
24. Mathurin P. HCV burden in Europe and the possible impact of current treatment. *Dig Liver Dis* 2013; 30: (45 Suppl 5): S314-7.
25. Kershenobich D, Razavi HA, Sánchez-Avila JF, Bessone F, Coelho HS, Dagher L, Gonçales FL, et al. Trends and projections of hepatitis C virus epidemiology in Latin America. *Liver Int* 2011; 31 (Suppl 2): S18-29.
26. Szabo SM, Bibby M, Yuan Y, Donato BM, Jiménez-Mendez R, Castañeda-Hernández G, Rodríguez-Torres M, et al. The epidemiologic burden of hepatitis C virus infection in Latin America. *Ann Hepatol* 2012; 11: 623-35.
27. Pereira LM, Martelli CM, Moreira RC, Merchan-Hamman E, Stein AT, Cardoso MR, Figueiredo GM, et al. Prevalence and risk factors of Hepatitis C virus infection in Brazil, 2005 through 2009: a cross-sectional study. *BMC Infect Dis* 2013; 13:60.
28. Davis KL, Mitra D, Medjedovic J, Beam C, Rustgi V. Direct economic burden of chronic hepatitis C virus in a United States managed care population. *J Clin Gastroenterol* 2011; 45: 17-24.
29. Razavi H, Elkhoury AC, Elbasha E, Estes C, Pasini K, Poynard T, Kumar R. Chronic hepatitis C virus (HCV) disease burden and cost in the United States. *Hepatology* 2013; 57: 2164-70.
30. Ward JW. The epidemiology of chronic hepatitis C and one-time hepatitis C virus testing of persons born during 1945 to 1965 in the United States. *Clin Liver Dis* 2013; 17: 1-11.
31. Schmidt AJ, Falcato L, Zahno B, Burri A, Regenass S, Müllhaupt B, Bruggmann P. Prevalence of hepatitis C in a Swiss sample of men who have sex with men: whom to screen for HCV infection? *BMC Public Health* 2014; 14: 3.
32. Larney S, Kopinski H, Beckwith CG, Zaller ND, Jarlais DD, Hagan H, Rich JD. Incidence and prevalence of hepatitis C in prisons and other closed settings: results of a systematic review and meta-analysis. *Hepatology* 2013; 58: 1215-24.
33. Bialek SR, Terrault NA. The changing epidemiology and natural history of hepatitis C virus infection. *Clin Liver Dis* 2006; 10: 697-715.

34. Centers for Disease Control and Prevention. Recommendations for prevention and control of hepatitis C virus (HCV) infections and HCV-related chronic disease. *MMWR Recomm Rep* 1998; 47: 1-39.
35. 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. U.S. Public Health Service (USPHS) and Infectious Diseases Society of America (IDSA). *MMWR Recomm Rep* 1999; 48: 1-59.
36. Ferreira A de S, Perez R de M, Ferraz ML, Lewis-Ximenez LL, Pereira JL, de Almeida PR, de Mattos AA, et al. Acute hepatitis C in Brazil: results of a national survey. *J Med Virol* 2011; 83: 1738-43.
37. Tovo CV, Dos Santos DE, de Mattos AZ, de Almeida PR, de Mattos AA, Santos BR. Ambulatorial prevalence of hepatitis B and C markers in patients with human immunodeficiency virus infection in a general hospital. *Arq Gastroenterol* 2006; 43: 73-6.
38. Denniston MM, Klevens RM, McQuillan GM, Jiles RB. Awareness of infection, knowledge of hepatitis C, and medical follow-up among individuals testing positive for hepatitis C: National Health and Nutrition Examination Survey 2001-2008. *Hepatology* 2012; 55: 1652-61.
39. Jacobson IM, Davis GL, El-Serag H, Negro F, Trépo C. Prevalence and challenges of liver diseases in patients with chronic hepatitis C virus infection. *Clin Gastroenterol Hepatol* 2010; 8: 924-33.
40. Davis GL, Alter MJ, El-Serag H, Poynard T, Jennings LW. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. *Gastroenterology* 2010; 138: 513-21.
41. Smith BD, Morgan RL, Beckett GA, Falck-Ytter Y, Holtzman D, Ward JW. Hepatitis C virus testing of persons born during 1945-1965: recommendations from the Centers for Disease Control and Prevention. *Ann Intern Med* 2012; 157: 817-22.
42. Smith BD, Morgan RL, Beckett GA, Falck-Ytter Y, Holtzman D, Teo CG, Jewett A, et al. Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945-1965. *MMWR Recomm Rep* 2012; 61: 1-32.
43. Mahajan R, Liu SJ, Klevens RM, Holmberg SD. Indications for testing among reported cases of HCV infection from enhanced hepatitis surveillance sites in the United States, 2004-2010. *Am J Public Health* 2013; 103: 1445-49.
44. Prati GM, Aghemo A, Rumi MG, D'Ambrosio R, De Nicola S, Donato MF, Degasperi E, et al. Hyporesponsiveness to PegIFN?2B plus ribavirin in patients with hepatitis C-related advanced fibrosis. *J Hepatol* 2012; 56: 341-7.
45. Williams MJ, Lang-Lenton M; Trent HCV Study Group. Progression of initially mild hepatic fibrosis in patients with chronic hepatitis C infection. *J Viral Hepat* 2011; 18: 17-22.
46. Sebastiani G, Alberti A. How far is noninvasive assessment of liver fibrosis from replacing liver biopsy in hepatitis C? *J Viral Hepat* 2012; 19 (Suppl 1): 18-32.
47. Gonzalez HC, Jafri SM, Gordon SC. Role of liver biopsy in the era of direct-acting antivirals. *Curr Gastroenterol Rep* 2013; 15(2): 307.
48. Colloredo G, Guido M, Sonzogni A, Leandro G. Impact of liver biopsy size on histological evaluation of chronic viral hepatitis: the smaller the sample the milder the disease. *J Hepatol* 2003; 39:239-44.
49. Bhogal H, Sterling RK. Staging of liver disease- which option is right for my patient? *Infect Dis Clin N Am* 2012; 26: 849-6.
50. Berzigotti A, Castera L. Hepatology snapshot- update on ultrasound imaging of liver fibrosis. *J Hepatol* 2013; 58: 180-2.
51. Ziol M, Handra-Luca A, Kettaneh A, Christidis C, Mal F, Kazemi F, de Lédinghen V, et al. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C. *Hepatology* 2005; 41: 48-54.
52. Friedrich-Rust M, Ong MF, Martens S, Sarrazin C, Bojunga J, Zeuzem S, Herrmann E. Performance of transient elastography for the staging of liver fibrosis: a meta-Analysis. *Gastroenterology* 2008; 134: 960-74.
53. Vergniol J, Foucher J, Terrebonne E, Bernard PH, le Bail B, Merrouche W, Couzigou P, et al. Noninvasive tests for fibrosis and liver stiffness predict 5-year outcomes of patients with chronic hepatitis C. *Gastroenterology* 2011; 140: 1970-9.
54. Lucidarme D, Foucher J, Le Bail B, Vergniol J, Castera L, Duburque C, Forzy G, et al. Factors of accuracy of transient elastography (fibroscan) for the diagnosis of liver fibrosis in chronic hepatitis C. *Hepatology* 2009; 49: 1083-9.
55. Castera L. Noninvasive methods to assess liver disease in patients with hepatitis B and C. *Gastroenterology* 2012; 142: 1293-300.
56. Bota S, Herkner H, Sporea I, Salzl P, Sirli R, Neghina AM, Peck-Radosavljevic M. Meta-analysis: ARFI elastography versus transient elastography for the evaluation of liver fibrosis. *Liver Int* 2013; 33: 1138-47.
57. Wang Q-B, Zhu H, Liu H-L, Zhang B. Performance of magnetic resonance elastography and diffusion-weighted imaging for the staging of hepatic fibrosis: a meta-analysis. *Hepatology* 2012; 56: 239-47.
58. Castéra L, Vergniol J, Foucher J, Le Bail B, Chanteloup E, Haaser M, Darriet M, et al. Prospective comparison of transient elastography, FibroTest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. *Gastroenterology* 2005; 128: 343-50.
59. Degos F, Perez P, Roche B, Mahmoudi A, Asselineau J, Voitot H, Bedossa P, 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: 1013-21.
60. Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, Lok AS. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology* 2003; 38: 518-26.
61. Vallet-Pichard A, Mallet V, Nalpas B, Verkarre V, Nalpas A, Dhalluin-Venier V, Fontaine H, et aL. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection: comparison with liver biopsy and fibrotest. *Hepatology* 2007; 46: 32-6.
62. Sebastiani G, Halfon P, Castera L, Pol S, Thomas DL, Mangia A, Di Marco V, et al. SAFE biopsy: a validated method for large-scale staging of liver fibrosis in chronic hepatitis C. *Hepatology* 2009; 49: 1821-7.
63. Boursier J, Vergniol J, Sawadogo A, Dakka T, Michalak S, Gallois Y, Le Tallec V, et al. The combination of a blood test and Fibroscan improves the non-invasive diagnosis of liver fibrosis. *Liver Int* 2009; 29: 1507-15.
64. Castera L, Forns X, Alberti A. Non-invasive evaluation of liver fibrosis using transient elastography. *J Hepatol* 2008; 48: 835-47.
65. Boursier J, de Ledinghen V, Zarski JP, Rousselet MC, Sturm N, Foucher J, Leroy V, et al. A new combination of blood test and fibroscan for accurate non-invasive diag-

nosis of liver fibrosis stages in chronic hepatitis C. *Am J Gastroenterol* 2011; 106: 1255-63.
66. AASLD, IDSA, IAS-USA. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org. (Accessed: 27/04/2014.)
67. EASL. Recommendations on treatment of hepatitis C. http://files.easl.eu/easl-recommendations-on-treatment-of-hepatitis-C/index.htm. (Accessed: 27/04/2014.)
68. Bruno S, Crosignani A, Facciotto C, Rossi S, Roffi L, Redaelli A, de Franchis R, et al. Sustained virologic response prevents the development of esophageal varices in compensated, Child-Pugh class A hepatitis C virus-induced cirrhosis. A 12-year prospective follow-up study. *Hepatology* 2010; 51: 2069-76.
69. Morgan TR, Ghany MG, Kim HY, Snow KK, Shiffman ML, De Santo JL, Lee WM, et al. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. *Hepatology* 2010; 52: 833-44.
70. Van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, Duarte-Rojo A, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA* 2012; 308: 2584-93.
71. Lemoine M, Nayagam S, Thursz M. Viral hepatitis in resource-limited countries and access to antiviral therapies: current and future challenges. Future Virol 2013; 8: 371-380.
72. Sitole M, Silva M, Spooner L, Comee MK, Malloy M. Telaprevir versus boceprevir in chronic hepatitis C: a meta-analysis of data from phase II and III trials. *Clin Ther* 2013; 35: 190-7.
73. Cooper C, Lester R, Thorlund K, Druyts E, El Khoury AC, Yaya S, Mills EJ. Direct-acting antiviral therapies for hepatitis C genotype 1 infection: a multiple treatment comparison meta-analysis. *QJM* 2013; 106: 153-63.
74. Sherman KE, Flamm SL, Afdhal NH, Nelson DR, Sulkowski MS, Everson GT, Fried MW, et al. Response-guided telaprevir combination treatment for hepatitis C virus infection. *N Engl J Med* 2011; 365: 1014-24.
75. Buti M, Agarwal K, Horsmans Y, Sievert W, Janczewska E, Zeuzem S, Nyberg L, et al. Telaprevir twice daily is noninferior to telaprevir every 8 hours for patients with chronic hepatitis C. *Gastroenterology* 2014; 146: 744-753.
76. Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, Schultz M, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med* 2013; 368: 1878-87.
77. Jacobson IM, Dore GJ, Foster GR, Fried MW, Radu M, Rafalsky VV, Moroz L, et al. Simeprevir with pegylated interferon alpha-2a plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-1): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet* 2014 Jun 3. [Epub ahead of print]
78. Manns M, Marcellin P, Poordad F, de Araujo ES. Simeprevir with pegylated interferon alpha-2a or 2b plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-2): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2014 Jun 3. [Epub ahead of print]
79. Alves R, Queiroz AT, Pessoa MG, da Silva EF, Mazo DF, Carrilho FJ, Carvalho-Filho RJ, et al. The presence of resistance mutations to protease and polymerase inhibitors in Hepatitis C virus sequences from the Los Alamos databank. *J Viral Hepat* 2013; 20: 414-21.
80. Forns X, Lawitz E, Zeuzem S, Gane E, Bronowicki JP, Andreone P, Horban A, et al. Simeprevir with peginterferon and ribavirin leads to high rates of SVR in patients with HCV genotype 1 who relapsed after previous therapy: A phase 3 trial. *Gastroenterology* 2014; 146: 1669-79.
81. Izumi N, Hayashi N, Kumada H, Okanoue T, Tsubouchi H, Yatsuhashi H, Kato M, et al. Once-daily simeprevir with peginterferon and ribavirin for treatment-experienced HCV genotype 1-infected patients in Japan: the CONCERTO-2 and CONCERTO-3 studies. *J Gastroenterol* 2014; 49: 941-53.
82. Sulkowski MS, Jacobson I, Ghalib R, et al. Once-daily simeprevir (TMC-435) plus sofosbuvir (GS-7977) with or without ribavirin in HCV genotype-1 prior null responders with METAVIR F0-2: COSMOS study subgroup analysis. 49th Annual Meeting of EASL. London, UK, April 9-13, 2014.
83. Lawitz M, Ghalib R, Rodriguez-Torres M, et al. Simeprevir plus sofosbuvir with/without ribavirin in HCV genotype-1 prior null-responder/treatment-naïve patients (COSMOS study): primary endpoint (SVR12) results in patients with METAVIR F3-4 (Cohort 2). 49th Annual Meeting of EASL. London, UK, April 9-13, 2014.
84. European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatitis C virus infection. *J Hepatol* 2011; 55: 245-64.
85. Jacobson I, Gordon S, Kowdley K, Yoshida E, Rodriguez Torres M, Sulkowski M. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. New Engl J Med 2013; 368: 1867-77.
86. Zeuzem S, Dusheiko G, Salupere R, Mangia A, Flisiak R, Hyland R, et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. New Engl J Med 2014; 370: 1993-2001.
87. Pawlotsky JM. NS5A inhibitors in the treatment of hepatitis C. *J Hepatol* 2013; 59 (2): 375-82.
88. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, Jacobson I, Lawitz E, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. *N Engl J Med* 2014; 370: 211-21.
89. Negro F, Alberti A. The global health burden of hepatitis C virus infection. *Liver Int* 2011; 31 (Suppl 2): 1-3.
90. Andriulli A, Dalgard O, Bjøro K, Mangia A. Short-term treatment duration for HCV-2 and HCV-3 infected patients. *Dig Liver Dis* 2006; 38: 741-8.
91. Marcellin P, Cheinquer H, Curescu M, Dusheiko GM, Ferenci P, Horban A, Jensen D, et al. High sustained virologic response rates in rapid virologic response patients in the large real-world PROPHESYS cohort confirm results from randomized clinical trials. *Hepatology (Baltimore, Md)* 2012; 56: 2039-2050.
92. Bühler S, Bartenschlager R. New targets for antiviral therapy of chronic hepatitis C. *Liver Int* 2012; 32 (Suppl 1): 9-16.
93. Poordad F, McCone J Jr, Bacon BR, Bruno S, Manns MP, Sulkowski MS, Jacobson IM, et al. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med*. 2011; 364: 1195-206.
94. Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, Marcellin P, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med*. 2011; 364: 2405-16.
95. Foster GR, Hézode C, Bronowicki JP, Carosi G, Weiland O, Verlinden L, van Heeswijk R, et al. Telaprevir alone or with peginterferon and ribavirin reduces HCV RNA in patients with chronic genotype 2 but not genotype 3 infections. *Gastroenterology* 2011; 141: 881-889.e1.
96. Silva MO, Treitel M, Graham DJ, Curry S, Frontera MJ, McMonagle P, Gupta S, et al. Antiviral activity of boce-

previr monotherapy in treatment-naive subjects with chronic hepatitis C genotype 2/3. *J Hepatol* 2013; 59: 31-7.
97. Dore GJ, Lawitz E, Hezode C, Shafran S, Ramji A, Tatum H. Daclatasvir combined with peginterferon alfa-2a and ribavirin for 12 or 16 weeks in patients with hepatitis C virus genotype 2 or 3 infection: COMMAND GT 2/3 Study. *J Hepatol* 2013; 58 (Suppl 1): S570.
98. Gane EJ, Stedman CA, Hyland RH, Ding X, Svarovskaia E, Symonds WT, Hindes RG, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. *N Engl J Med* 2013; 368: 34-44.
99. Lawitz E, Lalezari JP, Hassanein T, Kowdley KV, Poordad FF, Sheikh AM, Afdhal NH, et al. Sofosbuvir in combination with peginterferon alfa-2a and ribavirin for non-cirrhotic, treatment-naive patients with genotypes 1, 2, and 3 hepatitis C infection: a randomised, double-blind, phase 2 trial. *The Lancet Infectious Diseases* 2013;
100. Lawitz E, Poordad F, Brainard D, Hyland RH, An D, Symonds WT. Sofosbuvir in combination with PegIFN and ribavirin for 12 weeks provides high SVR rates in HCV-infected genotype 2 or 3 treatment-experienced patients with and without compensated cirrhosis: results from the LONESTAR-2 study . *Hepatology (Baltimore, Md)*. 2013; 58: (Supl 1) 1380A.
101. Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, Schultz M, et al. Sofosbuvir for Previously Untreated Chronic Hepatitis C Infection. *N Engl J Med*. 2013; 368: 1878-1887.
102. Jacobson IM, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, Shiffman ML, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med* 2013; 368: 1867-77.
103. Esteban R, Nyberg L, Lalezan J, Ni L, Doehle B, Kanwar B, et al. Successful retreatment with sofosbuvir-containing regimens for HCV genotype 2 or 3 infected patients who failed prior sofosbuvir plus ribavirin therapy. *J Hepatol* 2014; 60 (Suppl 1): S4.
104. Gane EJ, Hyland RH, An D, Pang PS, Symonds WT, Mchutchison JG, et al. Sofosbuvir/ledipasvir fixed dose combination is safe and effective in difficult-to-treat populations including genotype-3 patients, decompensated genotype-1 patients, and genotype-1 patients with prior sofosbuvir treatment experience. *J Hepatol* 2014; 60 (Suppl 1): S3.
105. Everson GT, Tran TT, Towner WJ, Davis MN, Wyles D, Nahass R, et al. Safety and efficacy of treatment with the interferon-free, ribavirin-free combination of sofosbuvir + GS-5816 for 12 weeks in the treatment naive patients with genotype 1-6 HCV infection. *J Hepatol* 2014; 60 (Suppl 1): S46.
106. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, Jacobson I, Lawitz E, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. *N Engl J Med* 2014; 370: 211-221.
107. Verbeeck J, Maes P, Lemey P, Pybus OG, Wollants E, Song E, Nevens F, et al. Investigating the origin and spread of hepatitis C virus genotype 5a. *J Virology* 2006; 80 (9): 4220-6.
108. Blackard JT, Shata MT, Shire NJ, Sherman KE. Acute hepatitis C virus infection: a chronic problem. *Hepatology*. 2008; 47: 321-31.
109. Williams I. Epidemiology of hepatitis C in the United States. *Am J Med* 1999; 107: 2S.
110. Armstrong GL, Alter MJ, McQuillan GM, Margolis HS. The past incidence of hepatitis C virus infection: implications for the future burden of chronic liver disease in the United States. *Hepatology* 2000; 31: 777.
111. Hoofnagle JH. Hepatitis C: the clinical spectrum of disease. *Hepatology* 1997; 26: 15S.
112. Farci P, Alter HJ, Wong D, Miller RH, Shih JW, Jett B, Purcell RH, et al. A long-term study of hepatitis C virus replication in non-A, non-B hepatitis. *N Engl J Med* 1991; 325: 98.
113. Wang TY, Kuo HT, Chen LC, Chen YT, Lin CN, Lee MM. Use of polymerase chain reaction for early detection and management of hepatitis C virus Ann Clin Lab Sci. 2002 Spring;32:137-41.
114. Maheshwari A, Thuluvath PJ. Management of acute hepatitis C. *Clin Liver Dis* 2010; 14: 169.
115. Beld M, Penning M, van Putten M, et al. Low levels of hepatitis C virus RNA in serum, plasma, and peripheral blood mononuclear cells of injecting drug users during long antibody-undetectable periods before seroconversion. *Blood* 1999; 94: 1183.
116. Wiese M, Grüngreiff K, Güthoff W, Lafrenz M, Oesen U, Porst H, et al. Outcome in a hepatitis C (genotype 1b) single source outbreak in Germany— a 25-year multicenter study. *J Hepatol* 2005; 43: 59.
117. Nikolaeva LI, Blokhina NP, Tsurikova NN, Voronkova NV, Miminoshvili MI, Braginsky DM, Yastrebova ON, et al. Virus-especific antibody titres in different phases of hepatitis C virus infection. *J Viral Hepat* 2002; 9: 429.
118. Wawrzynowicz-Syczewska M, Kubicka J, Lewandowski Z, Boro?-Kaczmarska A, Radkowski M, et al. Natural history of acute symptomatic hepatitis type C. Infection 2004; 32:138.
119. Loomba R, Rivera MM, McBurney R, Park Y, Haynes-Williams V, Rehermann B, Alter HJ, et al. The natural history of acute hepatitis C: clinical presentation, laboratory findings and treatment outcomes. *Aliment Pharmacol Ther* 2011; 33: 559.
120. Deterding K, Wiegand J, Grüner N, Hahn A, Jäckel E, Jung MC, Buggisch P, et al. The German Hep-Net acute hepatitis C cohort: impact of viral and host factors on the initial presentation of acute hepatitis C virus infection. *Z Gastroenterol* 2009; 47: 531
121. Gerlach JT, Diepolder HM, Zachoval R, Gruener NH, Jung MC, Ulsenheimer A, Schraut WW, et al. Acute Hepatitis: high rate of both spontaneous and treatment-induced viral clearance. *Gastroenterology* 2003; 125: 80.
122. Santantonio T, Sinisi E, Guastadisegni A, Casalino **C**, Mazzola M, Gentile A, Leandro G, et al. Natural course of acute hepatitis C: a long-term prospective study. *Dig Liver Dis* 2003; 35: 104.
123. Kenny-Walsh E. Clinical outcomes after hepatitis C infection from contaminated anti-D immune globulin. Irish Hepatology Research Group. *N Engl J Med* 1999; 340: 1228.
124. Missale G, Bertoni R, Lamonaca V, Valli A, Massari M, Mori C, Rumi MG, et al. Different clinical behaviors of acute hepatitis C virus infection are associated with different vigor of the anti-viral cell-mediated immune response. *J Clin Invest* 1996; 98: 706.
125. Diepolder HM, Zachoval R, Hoffmann RM, Wierenga EA, Santantonio T, Jung MC, Eichenlaub D, et al. Possible mechanism involving T-lymphocyte response to non-structural protein 3 in viral clearance in acute hepatitis C virus infection. *Lancet* 1995; 346: 1006.
126. Hofer H, Watkins-Riedel T, Janata O, Penner E, Holzmann H, Steindl-Munda P, Gangl A, Ferenci P. Spontaneous viral clearance in patients with acute hepatitis C can be predicted by repeated measurements of serum viral load. *Hepatology* 2003; 37: 60.

127. Wiese M, Berr F, Lafrenz M, Porst H, Oesen U. Low frequency of cirrhosis in a hepatitis C (genotype 1b) single-source outbreak in germany: a 20-year multicenter study. *Hepatology* 2000; 32: 91.
128. Rodger AJ, Roberts S, Lanigan A, Bowden S, Brown T, Crofts N. Assessment of long-term outcomes of community-acquired hepatitis C infection in a cohort with sera stored from 1971 to1975. *Hepatology* 2000; 32: 582.
129. Thomas DL, Astemborski J, Rai RM, Anania FA, Schaeffer M, Galai N, Nolt K, et al. The natural history of hepatitis C virus infection: host, viral, and environmental factors. *JAMA* 2000; 284: 450.
130. Villano SA, Vlahov D, Nelson KE, et al. Persistence of viremia and the importance of long-term follow-up after acute hepatitis C infection. *Hepatology* 1999; 29: 908.
131. Grebely J, Page K, Sacks-Davis R, van der Loeff MS, Rice TM, Bruneau J, Morris MD, et al. The effects of female sex, viral genotype, and IL28B genotype on spontaneous clearance of acute hepatitis C virus infection. *Hepatology* 2014; 59:109.
132. Corey KE, Mendez-Navarro J, Gorospe EC, Zheng H, Chung RT, et al. Early treatment improves outcomes in acute hepatitis C virus infection: a meta-analysis. *J Viral Hepat* 2010; 17: 201.
133. Dore GJ, Hellard M, Matthews GV, Grebely J, Haber PS, Petoumenos K, Yeung B, et al. Effective treatment of injecting drug users with recently acquired hepatitis C virus infection. *Gastroenterology* 2010; 138: 123.
134. Broers B, Helbling B, François A, Schmid P, Chuard C, Hadengue A, Negro F. Barriers to interferon-alpha therapy are higher in intravenous drug users than in other patients with acute hepatitis C. *J Hepatol* 2005; 42: 323.
135. Deterding K, Grüner N, Buggisch P, Wiegand J, Galle PR, Spengler U, Hinrichsen H, et al. Delayed versus immediate treatment for patients with acute hepatitis C: a randomised controlled non-inferiority trial. *Lancet Infect Dis* 2013; 13: 497.
136. Licata A, Di Bona D, Schepis F, Shahied L, Craxí A, Cammà C, et al. When and how to treat acute hepatitis C? *J Hepatol* 2003; 39: 1056.
137. Corey KE, Ross AS, Wurcel A, Schulze Zur Wiesch J, Kim AY, Lauer GM, Chung RT, et al. Outcomes and treatment of acute hepatitis C virus infection in United States population. *Clin Gastroenterol Hepatol* 2006; 4: 1278.
138. Kamal SM, Fouly AE, Kamel RR, Hockenjos B, Al Tawil A, Khalifa KE, He Q, et al. Peginterferon alpha-2b therapy in acute hepatitis C: impact of onset of therapy on sustained virologic response. *Gastroenterology* 2006; 130: 632.
139. Wiegand J, Buggisch P, Boecher W, Zeuzem S, Gelbmann CM, Berg T, Kauffmann W, et al. Early monotherapy with pegylated interferon alpha-2b of acute hepatitis C infection: the HEP-NET acute-HCV-II study. *Hepatology* 2006; 43: 250.
140. Santantonio T, Fasano M, Sinisi E, Guastadisegni A, Casalino C, Mazzola M, Francavilla R, et al. Efficacy of a 24-week course of PEG-IFN alpha-2b monotherapy in patients with acute hepatitis C after failure of spontaneous clearance. *J Hepatol* 2005; 42: 329.
141. Jaeckel E, Cornberg M, Wedemeyer H, Santantonio T, Mayer J, Zankel M, Pastore G, et al. Treatment of acute hepatitis C with interferon alfa-2b. *N Engl J Med* 2001; 345: 1452.
142. Nunnari G, Montineri A, Portelli V, Savalli F, Fatuzzo F, Cacopardo B. The use of peginterferon in monotherapy or in combination with ribavirin for the treatment of acute hepatitis C. *Eur Rev Med Pharmacol Sci* 2012; 16: 1013.
143. Kamal SM, Ismail A, Graham CS, He Q, Rasenack JW, Peters T, Tawil AA, et al. Pegylated interferon alpha therapy in acute hepatitis C: realtion to hepatitis C virus-specific T cell response kinetics. *Hepatology* 2004; 39: 1721.
144. Serpaggi J, Chaix ML, Batisse D, Dupont C, Vallet-Pichard A, Fontaine H, Viard JP. et al. Sexually transmitted acute infection with a clustered genotype 4 hepatitis C virus in HIV-1-infected men and inefficacy of early antiviral therapy. *AIDS* 2006; 20: 233.
145. Danta M, Dusheiko GM. Acute HCV in HIV-positive individuals - a review. Curr Pharm Des 2008; 14: 1690.
146. Laguno M, Martínez-Rebollar M, Perez I, Costa J, Larrousse M, Calvo M, Loncá M, et al. Low rate of sustained virological response in an outbreak of acute hepatitis C in HIV-infected patients. *AIDS Res Hum Retrov* 2012; 28: 1294.
147. Matthews GV, Hellard M, Haber P, Yeung B, Marks P, Baker D, McCaughan G, et al. Characteristics and treatment outcomes among HIV-infected individuals in the Australian Trail in Acute Hepatitis C. Clin Infect Dis 2009; 48: 650.
148. Dominguez S, Ghosn J, Valantin MA, Schruniger A, Simon A, Bonnard P, Caumes E, et al. Efficacy of early treatment of acute hepatitis C infection with pegylated interferon and ribavirin in HIV-infected patients. *AIDS* 2006; 20: 1157.
149. Piroth L, Larsen C, Binquet C, Alric L, Auperin I, Chaix ML, Dominguez S, et al. Treatment of acute hepatitis C in human immunodeficiency virus-infected patients: the HEPAIG study. *Hepatology* 2010; 52: 1915.
150. Fierer DS, Dieterich DT, Mullen MP, Branch AD, Uriel AJ, Carriero DC, van Seggelen WO, et al. Telaprevir in the treatment of acute hepatitis C virus infection in HIV-infected men. Clin Infect Dis 2014; 58: 873.
151. Kamal SM, Moustafa KN, Chen J, Fehr J, Abdel Moneim A, Khalifa KE, El Gohary LA, et al. Duration of peginterferon therapy in acute hepatitis C: a randomized trial. *Hepatology* 2006; 43:923.
152. Hézode C, Fontaine H, Dorival C, Zoulim F, Larrey D, Canva V, De Ledinghen V, et al. CUPIC Study Group. Effectiveness of telaprevir or boceprevir in treatment-experienced patients with HCV genotype 1 infection and cirrhosis. *Gastroenterology* 2014; 147: 132-142.
153. Saxena V, Manos MM, Yee HS, Catalli L, Wayne E, Murphy RC, Shvachko VA, et al. Telaprevir or boceprevir triple therapy in patients with chronic hepatitis C and varying severity of cirrhosis. *Aliment Pharmacol Ther*. 2014; 39: 1213-24.
154. Latin American Association for the Study of the Liver Practice Guidelines. Diagnosis, management, and treatment of hepatitis C. *Ann Hepatol* 2010; 9 (Suppl): 8-26.
155. Jacobson IM, Dore GJ, Foster G, et al. Simeprevir (TMC435) with peginterferon/ribavirin for chronic HCV genotype-1 infection in treatment-naïve patients: results from QUEST-1, a phase III trial. Digestive Disease Week, May 18-21, 2013; Orlando, FL.
156. Poordad F, Manns MP, Marcellin P, et al. Simeprevir (TMC435) with peginterferon/ribavirin for treatment of chronic HCV genotype-1 infection in treatment-naïve patients: results from QUEST-2, a phase III trial. Digestive Disease Week, May 18-21, 2013; Orlando, FL.
157. Pessôa MG, Mazo DF, De Carvalho IMVG, Carrilho FJ. (Resistant associated variants to protease inhibitors in Brazil)

Mutações de resistência aos inibidores de protease no Brasil. Review article. *Rev Panam Infectol* 2014; 16(1): 57-61
158. Forns X, Lawitz E, Zeuzem S, et al. Simeprevir (TMC435) with peg-interferon a-2a/ribavirin for treatment of chronic HCV genotype 1 infection in patients who relapsed after previous interferon-based therapy: efficacy and safety in patient sub-populations in the PROMISE phase III trial. 64th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD 2013). Nov 1-5, 2013, 2013b; Washington, DC.
159. Jacobson IM, Ghalib RH, Rodriguez-Torres M, et al. SVR results of a once-daily regimen of simeprevir (TMC435) plus sofosbuvir (GS-7977) with or without ribavirin in cirrhotic and non-cirrhotic HCV genotype 1 treatment-nai?ve and prior null responder patients: the COSMOS study. Hepatology: special issue: The 64th Annual Meeting of the American Association for the Study of Liver Diseases: the Liver Meeting 2013. 2013; 58(4): 1379A.
160. Lawitz E, Poordad F, Membreno FE, et al. Once daily sofosbuvir/ledipasvir fixed dose combination with or without ribavirin resulted in ?95% sustained virologic response in patients with HCV genotype 1, including patients with cirrhosis: the LONESTAR trial. Program and abstracts of the 64th Annual Meeting of the American Association for the Study of Liver Diseases; November 1-5, 2013; Washington, DC. 215A.
161. Forman LM, Lewis JD, Berlin JA, Feldman HI, Lucey MR. et al. The association between hepatitis C infection and survival after orthotopic liver *Transplantation*. *Gastroenterology* 2002; 122: 889-96.
162. Garcia-Retortillo M, Forns X, Feliu A, Moitinho E, Costa J, Navasa M, Rimola A, et al. Hepatitis C virus kinetics during and immediately after liver *Transplantation*. *Hepatology* 2002; 35: 680-7.
163. Peng CY, Chien RN, Liaw YF. Hepatitis B virus-related decompensated liver cirrhosis: benefits of antiviral therapy. *J Hepatol* 2012; 57(2): 442-50.
164. Forns X, García-Retortillo M, Serrano T, Feliu A, Suarez F, de la Mata M, García-Valdecasas JC, et al. Antiviral therapy of patients with decompensated cirrhosis to prevent recurrence of hepatitis C after liver *Transplantation*. *J Hepatol* 2003; 39(3): 389-96.
165. Carrión JA, Martínez-Bauer E, Crespo G, Ramírez S, Pérez-del-Pulgar S, García-Valdecasas JC, Navasa M, 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(4): 719-28.
166. Everson GT, Terrault NA, Lok AS, et al. Adult-to-adult living donor liver *Transplantation* cohort study. A randomized controlled trial of pretransplant antiviral therapy to prevent recurrence of hepatitis C after liver *Transplantation*. *Hepatology* 2013; 57(5): 1752-62.
167. Fontaine H, Hezode C, Dorival C, et al. SVR12 rates and safety of triple therapy including telaprevir or boceprevir in 221 cirrhotic non-responders treated in the French Early Access Program (ANRSCO20-CUPIC). *J Hepatol* 2013; 58: S27.
168. Hézode C, Fontaine H, Dorival C, Larrey D, Zoulim F, Canva V, de Ledinghen V, et al. CUPIC study group. Triple therapy in treatment-experienced patients with HCV-cirrhosis in a multicentre cohort of the French Early Access Programme (ANRSCO20-CUPIC)-NCT01514890. *J Hepatol* 2013; 59(3): 434-41.
169. Verna EC, Terry N, Lukose T, et al. High early response rates with protease inhibitor triple therapy in a multicenter cohort of HCV infected patients awaiting liver *Transplantation*. *Hepatology* 2012; 56(Suppl 1): 218A.
170. Curry MP, Forns X, Chung RT, et al. Pretransplant sofosbuvir and ribavirin to prevent recurrence of HCV infection after liver *Transplantation*. *Hepatology* 2013; 58 (Suppl 1): 314A.
171. Lens S, Gambato M, Londoño MC, Forns X. Interferon-free regimens in the liver-transplant setting. *Semin Liver Dis* 2014; 34: 58-71.
172. Charlton M, Ruppert K, Belle SH, et al. Long-term results and modeling to predict outcomes in recipients with HCV infection: results of the NIDDK liver *Transplantation* database. Liver Transpl 2004; 10: 1120-30.
173. Berenguer M, Prieto M, Rayón JM, Mora J, Pastor M, Ortiz V, Carrasco D, et al. Natural history of clinically compensated hepatitis C virus-related graft cirrhosis after liver *Transplantation*. *Hepatology* 2000; 1: 852-8.
174. Gane EJ. The natural history of recurrent hepatitis C and what influences this. Liver Transpl 2008; 14 (Suppl 2): S36- 44.
175. Berenguer M, Mccaughan G. Hepatitis C virus-associated cholestatic hepatitis: we cannot seem to agree on diagnostic criteria. Liver Transpl 2013; 19: 115-7.
176. Roche B, Sebagh M, Canfora ML, Antonini T, Roque-Afonso AM, Delvart V, Saliba F, et al. Hepatitis C virus therapy in liver transplant recipients: response predictors, effect on fibrosis progression, and importance of the initial stage of fibrosis. Liver Transpl 2008; 14: 1766-77.
177. Mazzaferro V, Tagger A, Schiavo M, Regalia E, Pulvirenti A, Ribero ML, Coppa J, et al. Prevention of recurrent hepatitis C after liver *Transplantation* with early interferon and ribavirin treatment. *Transplant Proc* 2001; 33: 1355-7.
178. Chalasani N, Manzarbeitia C, Ferenci P, Vogel W, Fontana RJ, Voigt M, Riely C, et al. Peginterferon alpha-2a for hepatitis C after liver *Transplantation*: 2 randomized, controlled trials. *Hepatology* 2005; 41: 289-98.
179. Bzowej N, Nelson DR, Terrault NA, Everson GT, Teng LL, Prabhakar A, Charlton MR. PHOENIX: a randomized controlled trial of peginterferon alpha-2a plus ribavirin as a prophylactic treatment after liver *Transplantation* for hepatitis C virus. Liver Transpl 2011; 17: 528-38.
180. Shergill AK, Khalili M, Straley S, Bollinger K, Roberts JP, Ascher NA, Terrault NA, et al. Applicability, tolerability and efficacy of preemptive antiviral therapy in hepatitis C-infected patients undergoing liver *Transplantation*. Am J Transplant 2005; 5: 118-24.
181. Sugawara Y, Makuuchi M, Matsui Y, Kishi Y, Akamatsu N, Kaneko J, Kokudo N, et al. Preemptive therapy for hepatitis C virus after living-donor liver *Transplantation*. *Transplantation* 2004; 78: 1308-11.
182. Carrión JA, Torres F, Crespo G, Miquel R, García-Valdecasas JC, Navasa M, Forns X. Liver stiffness identifies two different patterns of fibrosis progression in patients with hepatitis C virus recurrence after liver *Transplantation*. *Hepatology* 2010; 51: 23-34.
183. Blasco A, Forns X, Carrión JA, García-Pagán JC, Gilabert R, Rimola A, Miquel R, et al. Hepatic venous pressure gradient identifies patients at risk of severe hepatitis C recurrence after liver *Transplantation*. *Hepatology* 2006; 43: 492-9.
184. Berenguer M. Systematic review of the treatment of established recurrent hepatitis C with pegylated interferon in combination with ribavirin. *J Hepatol* 2008; 49: 274-87.
185. Wang CS, Ko HH, Yoshida EM, Marra CA, Richardson K. Interferon-based combination anti-viral therapy for

hepatitis C virus after liver *Transplantation*: a review and quantitative analysis. Am J Transplant 2006; 6: 1586-99.
186. Xirouchakis E, Triantos C, Manousou P, Sigalas A, Calvaruso V, Corbani A, Leandro G, et al. Pegylated interferon and ribavirin in liver transplant candidates and recipients with HCV cirrhosis: systematic review and meta-analysis of prospective controlled studies. *J Viral Hepat* 2008; 15: 699-709.
187. Coilly A, Roche B, Dumortier J, et al. Safety and efficacy of protease inhibitors to treat hepatitis C after liver *Transplantation*, a multicenter experience. *J Hepatol* 2013; doi:10.1016/j.jhep.2013.08.018. (in press).
188. Pungpapong S, Aqel BA, Koning L, Murphy JL, Henry TM, Ryland KL, Yataco ML, et al. Multicenter experience using telaprevir or boceprevir with peginterferon and ribavirin to treat hepatitis C genotype 1 after liver *Transplantation*. Liver Transpl 2013; 19: 690-700.
189. Werner CR, Egetemeyr DP, Lauer UM, Nadalin S, Königsrainer A, Malek NP, Berg CP, et al. Telaprevir based triple therapy in liver transplant patients with hepatitis C virus: a 12-week pilot study providing safety and efficacy data. Liver Transpl 2012; 18: 1464-70.
190. Samuel D, Charlton M, Gane E, et al. Sofosbuvir and ribavirin for the treatment of recurrent hepatitis C infection after liver *Transplantation*: results of a prospective, multicenter study. 49th European Association for the Study of the *Liver Int*ernational Liver Congress (EASL 2014). London, April 9-13, 2014. Abstract, P1232.
191. Fontana RJ, Hughes EA, Bifano M, Appelman H, Dimitrova D, Hindes R, Symonds WT. Sofosbuvir and daclatasvir combination therapy in a liver transplant recipient with severe recurrent cholestatic hepatitis C. Am J Transplant 2013; 13: 1601-5.
192. Hernandez MD, Sherman KE. HIV/hepatitis C coinfection natural history and disease progression. Curr Opin HIV *AIDS* 2011; 6(6): 478-82.
193. Graham CS, Baden LR, Yu E, Mrus JM, Carnie J, Heeren T, Koziel MJ. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. Clin Infect Dis 2001; 15, 33 (4): 562-9.
194. European AIDS Clinical Society. Guidelines, version 7.0. October 2013. http://www.eacsociety.org/Portals/0/Guidelines_Online_131014.pdf (Accessed on May 25, 2014).
195. Macías J, Márquez M, Merino D, et al. Short-term risk of decompensation among HIV/HCV-coinfected patients with significant fibrosis. 21st Conference on Retroviruses and Opportunistic Infections (CROI 2014). Boston, March 3-6. Abstract 646.
196. Mendes-Corrêa M, Núñez M. Management of HIV and hepatitis virus coinfection. Expert Opin Pharmacother 2010; 11(15): 2497-516.
197. Telaprevir prescription information: access June 2014. http://www.janssen.com.au/files/Products/Incivo_PI.pdf?ac941bb8343879d4b017c876e58d73aa.
198. Boceprevir prescription information: access June 2014. http://www.merck.com/product/usa/pi_circulars/v/victrelis/victrelis_pi.pdf.
199. Dieterich D, Rockstroh J, Orkin C, et al. Simeprevir (TMC435) plus peg-IFN/ribavirin in HCV genotype-1/HIV-1 coinfection (Study C212). 21st Conference on retroviruses and opportunistic infections, March 3-6, 2014; abstract 24.
200. Simeprevir prescription information: access june 2014.
201. Rodriguez-Torres M, Rodriguez-Orengo J, Gaggar A, et al. Sofosbuvir and peginterferon alpha-2a/ribavirin for treatment-naïve genotype 1-4 HCV infected patients who are HIV coinfected with HIV. ID Week 2013; abstract 714.
202. Lawitz E, et al. Simeprevir plus sofosbuvir with/without ribavirin in HCV genotype 1 prior null-responder/treatment-naïve patients (COSMOS study): primary endpoint (SVR12) results in patients with Metavir F3-4 (cohort 2). 49th EASL. Abstract 165.
203. Naggie S, Sulkowski M, Lalezari J, et al. Sofosbuvir plus ribavirin for HCV genotype 1-3 infection in HIV coinfected patients (PHOTON-1). CROI 2014. Conference on retroviruses and opportunistic infections. Abstract 26.
204. Lacombe K, Valin N, Stitou H, Gozlan J, Thibault V, Boyd A, Poirier JM, et al. Efficacy and tolerance of telaprevir in HIV-hepatitis C virus genotype 1-coinfected patients failing previous antihepatitis C virus therapy: 24-week results. *AIDS* 2013; 27(8): 1356-9.
205. Cachay ER, Wyles DL, Torriani FJ, Ballard C, Colwell B, Lin JC, et al. High incidence of serious adverse events in HIV-infected patients treated with a telaprevir-based hepatitis C virus treatment regimen. *AIDS* 2013; 27:000-000. *AIDS*. 2013 Jul 24. [Epub ahead of print] PMID:23842130.
206. Genebat M, Vera F, Hernández-Quero J, Domingo P, Guardiola JM, Martínez-Madrid O, Martínez L, et al. Efficacy and tolerability after 24 weeks of treatment with telaprevir, pegylated interferon and ribavirin in cirrhotic HIV-HCV coinfected subjects. Antiviral Res 2014; 104: 59-61.
207. Martel-Laferrière V, Brinkley S, Bichoupan K, Posner S, Stivala A, Perumalswami P, Schiano T, et al. Virological response rates for telaprevir-based hepatitis C triple therapy in patients with and without HIV coinfection. HIV Med 2014; 15(2): 108-15.
208. http://www.hep-druginteractions.org/
209. Sofosbuvir prescription information: access June 2014. http://www.gilead.com/~/media/Files/pdfs/medicines/liver disease/sovaldi/sovaldi_pi.pdf.
210. Zarski JP, Bohn B, Bastie A, Pawlotsky JM, Baud M, Bost-Bezeaux F, Tran van Nhieu J, et al. Characteristics of patients with dual infection by hepatitis B and C viruses. *J Hepatol* 1998; 28: 27-33.
211. Chen DS, Kuo GC, Sung JL, Lai MY, Sheu JC, Chen PJ, Yang PM, et al. Hepatitis C virus infection in an area hyperendemic for hepatitis B and chronic liver disease: the Taiwan experience. J Infect Dis 1990; 162(4): 817-22.
212. Pallas JR, Farinas-Alvarez C, Prieto D, Delgado-Rodríguez M. Co-infections by HIV, hepatitis B and hepatitis C in imprisoned injecting drug users. Eur J Epidemiol 1999; 15: 699-704.
213. Gentile I, Di Flumeri G, Scarica S, Frangiosa A, Foggia M, Reynaud L, Borgia G, et al. Acute hepatitis C in patients undergoing hemodialysis: experience with high-dose interferon therapy. Minerva Urol Nefrol 2013; 65: 83-4.
214. Zhou J, Dore GJ, Zhang F, Lim PL, Chen YM. TREAT Asia HIV Observational Database. Hepatitis B and C virus coinfection in the TREAT Asia HIV observational database. *J Gastroenterol* Hepatol 2007; 22: 1510-8.
215. Mimms LT, Mosley JW, Hollinger FB, Aach RD, Stevens CE, Cunningham M, Vallari DV. Effect of concurrent acute infection with hepatitis C virus on acute hepatitis B virus infection. BMJ 1993; 307: 1095-7.
216. Yan BM, Lee SS. Acute coinfection with hepatitis B and hepatitis C viruses. *Can J Gastroenterol* 2005; 19(12): 729-30.

217. Sagnelli E, Coppola N, Pisaturo M, Masiello A, Tonziello G, Sagnelli C, Messina V. HBV superinfection in HCV chronic carriers: a disease that is frequently severe but associated with the eradication of HCV. *Hepatology* 2009; 49(4): 1090-7.
218. Potthoff A, Wedemeyer H, Boecher WO, Berg T, Zeuzem S, Arnold J, Spengler U, et al. Hep-Net B/C co-infection study group. The Hep-Net B/C co-infection trial: a prospective multicenter study to investigate the efficacy of pegylated interferon-alpha2b and ribavirin in patients with with HBV/HCV co-infection. *J Hepatol* 2008; 49(5): 688-94.
219. Raimondo G, Brunetto MR, Pontisso P, Smedile A, Maina AM, Saitta C, Squadrito G, et al. Longitudinal evaluation reveals a complex spectrum of virological profiles in hepatitis B virus/hepatitis C virus-coinfected patients. *Hepatology* 2006; 43: 100-7.
220. Brass V, Moradpour D. New insights into hepatitis B and C virus co-infection. *J Hepatol* 2009; 51(3): 423-5.
221. Liaw YF, Kao JH, Piratvisuth T, et al. Asian-Pacific consensus statement on the management of chronic hepatitis B: 2012 update. Hepatol Int 2012; 6: 531-61.
222. Gadano A, Daruich J, Cheinquer H, Faimboin H, Pessoa M, Tanno H, Mattos A, et al. Latin American guideline for the management of chronic hepatitis B. *Acta Gastroenterol Latinoam* 2011; 41(4): 340-50.
223. Villa E, Grottola A, Buttafoco P, Colantoni A, Bagni A, Ferretti I, Cremonini C, et al. High doses of alpha-interferon are required in chronic hepatitis due to coinfection with hepatitis B virus and hepatitis C virus: long term results of a prospective randomized trial *Am J Gastroenterol*. 2001; 96: 2973-7.
224. Liu CJ, Chuang WL, Lee CM, et al. An open label, comparative, multicenter study of peginterferon alpha-2a plus ribavirin in the treatment of patients with chronic hepatitis C/hepatitis B co-infection versus those with chronic hepatitis C monoinfection. *Gastroenterology* 2009; 136: 496-504.
225. Liu CJ, Chu YT, Shau WY, Kuo RN, Chen PJ, Lai MS. Treatment of patients with dual hepatitis C and B by peginterferon alpha and ribavirin reduced risk of hepatocellular carcinoma and mortality. Gut 2014; 63(3): 506-14.
226. Yu ML, Lee CM, Chen CL, Chuang WL, Lu SN, Liu CH, Wu SS, et al. Sustained HCV clearance and increased HBsAg seroclearance in patients with dual chronic hepatitis C and B during post-treatment follow-up. *Hepatology* 2013; 57: 2135-42.
227. Sagnelli E, Pisaturo M, Martini S, Sagnelli C, Filippini P, Coppola N, et al. Advances in the treatment of hepatitis B virus/hepatitis C virus coinfection. Expert Opin Pharmacother 2014; 15(10): 1337-49.
228. Yu ML, Lee CM, Chuang WL, Lu SN, Dai CY, Huang JF, Lin ZY, et al. HBsAg profiles in patients receiving peginterferon alpha-2a plus ribavirin for the treatment of dual chronic infection with hepatitis B and C viruses. J Infect Dis 2010; 202(1): 86-92.
229. Yu JW, Sun LJ, Zhao YH, Kang P, Gao J, Li SC. Analysis of the efficacy of treatment with peginterferon alpha-2a and ribavirin in patients coinfected with hepatitis B virus and hepatitis C virus. *Liver Int* 2009; 29(10): 1485-93.
230. Bergman S, Accortt N, Turner A, Glaze J. Hepatitis C infection is acquired pre-ESRD. *Am J Kidney Dis* 2005; 45: 684-9.
231. Ilcöl B, Ozener C, Avsar M Ilcol Y, Lawrence R, Ozer A, Cirakoğlu B, Akoğlu E. Hepatitis C infection in patients with chronic renal failure receiving conservative therapy [letter]. *Nephrol Dial Transplant* 1997; 12: 626.
232. Kumar H, Naqvi SA, Ahmed A, Hamid S. Hepatitis-C virus antibodies (anti-HCV) in haemodialyzed vs non- dialyzed patients. J Pak Med Assoc 1994; 44: 28-30.
233. Fabrizi F, Marcelli D, Bacchini G, Guarnori I, Erba G, Locatelli F. Antibodies to hepatitis C virus (HCV) in chronic renal failure (CRF) patients on conservative therapy: prevalence, risk factors and relationship to liver disease. *Nephrol Dial Transplant* 1994; 9: 780.
234. Lemos LB, Perez RM, Lemos MM, Draibe SA, Silva IS, Silva AE, Ferraz ML. Hepatitis C among predialysis patients: prevalence and characteristics in a large cohort of patients. *Nephron Clin Pract* 2008; 108(2): c135-40.
235. Lemos LB, Perez RM, Lemos MM, Lanzoni VP, Draibe SA, Silva IS, Silva AE, et al. Hepatitis C in chronic kidney disease: predialysis patients present more severe histological liver injury than hemodialysis patients? Am *J Nephrol* 2007; 27(2): 191-6.
236. Martin P, Carter D, Fabrizi F, Dixit V, Conrad AJ, Artinian L, Peacock V, et al. Histopathological features of hepatitis C in renal transplant candidates. *Transplantation* 2000; 69: 1479-84.
237. National Kidney Foundation, 2002. KDOQI clinical practice guidelines for chronic kidney disease.
238. Liu CH, Huang CF, Liu CJ, Dai CY, Liang CC, Huang JF, Hung PH, et al. Pegylated interferon-alpha2a with or without low-dose ribavirin for treatment-naïve patients with hepatitis C virus genotype 1 receiving hemodialysis: a randomized trial. *Ann Intern Med* 2013; 159: 729-38.
239. Bassu PP, Siriki R, Shah NJ, et al. Telaprevir with adjusted dose of ribavirin in naïve CHC-G1: efficacy and treatment in CHC in hemodialysis population. Target C (RCT). *J Hepatol* 2013: 58: S301-S31.
240. Treitel M, Marbury T, Preston RA, et al. Single-dose pharmacokinetics of boceprevir in subjects with impaired hepatic or renal function. *Clin Pharmacokinet* 2012; 51: 619-28.
241. Van Heeswijk R, Vandevoorde A, Boogaerts G, et al. The effect of severe renal impairment on the pharmacokinetics of the investigational HCV protease inhibitor telaprevir. *J Hepatol* 2011; 54: S492.
242. De Kanter CT, Drenth JP, Arends JE, Reesink HW, van der Valk M, de Knegt RJ, Burger DM. Viral hepatitis C therapy: pharmacokinetic and pharmacodynamic considerations. *Clin Pharmacokinet* 2014; 53(5): 409-27.
243. Finelli L, Miller JT, Tokars JI, Alter MJ, Arduino MJ. National surveillance of dialysis-associated diseases in the United States, 2002. *Semin Dial* 2005; 18: 52-61.
244. Othman B, Monem F. Prevalence of antibodies to hepatitis C virus among hemodialysis patients in Damascus, Syria. Infection 2001; 29: 262-5.
245. Abbott KC, Bucci JR, Matsumoto CS, Swanson SJ, Agodoa LY, Holtzmuller KC, Cruess DF, et al. Hepatitis C and renal *Transplantation* in the era of modern immunosuppression. *J Am Soc Nephrol* 2003; 14: 2908-18.
246. De Jesus Rodrigues de Freitas M, Fecury AA, de Almeida MK, Freitas AS, de Souza Guimaraes V, da Silva AM, da Costa RA, et al. Prevalence of hepatitis C virus infection and genotypes in patient with chronic kidney disease undergoing hemodialysis. *J Med Virol* 2013; 85: 1741-5.
247. Mendez-Sanchez N, Motola-Kuba D, Chavez-Tapia NC, Bahena J, Correa-Rotter R, Uribe M. 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.

248. Beltran M, Navas MC, De la Hoz F, Mercedes Munoz M, Jaramillo S, Estrada C, et al. Hepatitis C virus seroprevalence in multi-transfused patients in Colombia. *J Clin Virol* 2005; 34 (Suppl 2): S33-8.
249. Monsalve-Castillo F, Gomez-Gamboa L, Chacin-Bonilla L, Porto-Espinoza L, Costa-Leon L. Hepatitis C virus infection in hemodialysis patients in Maracaibo, Venezuela. *Rev Inst Med Trop Sao Paulo* 2012; 54: 53-5.
250. Curciarello JO, Adrover RE, Chiera AO, Touceda LA, Giammona AM, Raimondi JC, Fassi JC. Hepatitis C viruses antibodies. Prevalence and their influence on morbidity-mortality in renal transplant recipients, in the last two years of the kidney *Transplantation* program in La Plata city. *Acta Gastroenterol Latinoam* 1996; 26: 79-83.
251. Fabrizi F, Martin P, Dixit V, Bunnapradist S, Dulai G. Meta-analysis: effect of hepatitis C virus infection on mortality in dialysis. *Aliment Pharmacol Ther* 2004; 20: 1271-7.
252. Zylberberg H, Nalpas B, Carnot F, Skhiri H, Fontaine H, Legendre C, Kreis H, et al. Severe evolution of chronic hepatitis C in renal *Transplantation*: a case control study. *Nephrol Dial Transplant* 2002; 17: 129-33.
253. Okoh EJ, Bucci JR, Simon JF, Harrison SA. HCV in patients with end-stage renal disease. *Am J Gastroenterol* 2008; 103: 2123-34.
254. Baid-Agrawal S, Pascual M, Moradpour D, Frei U, Tolkoff-Rubin N. Hepatitis C virus infection in haemodialysis and kidney transplant patients. *Rev Med Virol* 2008; 18: 97-115.
255. KDIGO. Kidney disease: improving global O. KDIGO clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of hepatitis C in chronic kidney disease. *Kidney Int Suppl* 2008; 109: S1-99.
256. Terrault NA, Adey DB. The kidney transplant recipient with hepatitis C infection: pre- and post-*Transplantation* treatment. Clin *J Am Soc Nephrol* 2007; 2: 563-75.
257. Mikolasevic I, Racki S, Lukenda V, Milic S, Pavletic-Persic M, Orlic L. Nonalcoholic fatty liver disease in renal transplant recipients proven by transient elastography. *Transplant Proc* 2014; 46: 1347-52.
258. Fabrizi F, Dulai G, Dixit V, Bunnapradist S, Martin P. Meta-analysis: interferon for the treatment of chronic hepatitis C in dialysis patients. *Aliment Pharmacol Ther* 2003; 18: 1071-81.
259. Russo MW, Goldsweig CD, Jacobson IM, Brown RS, Jr. Interferon monotherapy for dialysis patients with chronic hepatitis C: an analysis of the literature on efficacy and safety. *Am J Gastroenterol* 2003; 98: 1610-5.
260. Bruchfeld A, Stahle L, Andersson J, Schvarcz R. Ribavirin treatment in dialysis patients with chronic hepatitis C virus infection- a pilot study. *J Viral Hepat* 2001; 8: 287-92.
261. Bruchfeld A, Lindahl K, Reichard O, Carlsson T, Schvarcz R. Pegylated interferon and ribavirin treatment for hepatitis C in haemodialysis patients. *J Viral Hepat* 2006; 13: 316-21.
262. Tan AC, Brouwer JT, Glue P, van Leusen R, Kauffmann RH, Schalm SW, de Vries RA, et al. Safety of interferon and ribavirin therapy in haemodialysis patients with chronic hepatitis C: results of a pilot study. *Nephrol Dial Transplant* 2001; 16: 193-5.
263. Covic A, Maftei ID, Mardare NG, Ionita-Radu F, Totolici C, Tuta L, Golea O, et al. Analysis of safety and efficacy of pegylated-interferon alpha-2a in hepatitis C virus positive hemodialysis patients: results from a large, multicenter audit. *J Nephrol* 2006; 19: 794-801.
264. Gordon CE, Uhlig K, Lau J, Schmid CH, Levey AS, Wong JB. Interferon treatment in hemodialysis patients with chronic hepatitis C virus infection: a systematic review of the literature and meta-analysis of treatment efficacy and harms. *Am J Kidney Dis* 2008; 51: 263-77.
265. Glue P. The clinical pharmacology of ribavirin. *Semin Liver Dis* 1999; 19 (Suppl 1): 17-24.
266. Dumortier J, Guillaud O, Gagnieu MC, Janbon B, Juillard L, Morelon E, Leroy V, et al. Anti-viral triple therapy with telaprevir in haemodialysed HCV patients: is it feasible? *J Clin Virol* 2013; 56: 146-9.
267. Donahue JG, Muñoz A, Ness PM, Brown DE Jr, Yawn DH, McAllister HA Jr, Reitz BA, et al. The declining risk of post-transfusion hepatitis C virus infection. *N Engl J Med* 1992; 327: 369-73.
268. Natov SN, Lau JY, Bouthot BA, Murthy BV, Ruthazer R, Schmid CH, Levey AS, et al. Serologic and virologic profiles of hepatitis C infection in renal transplant candidates. New England Organ Bank Hepatitis C Study Group. *Am J Kidney Dis* 1998; 31: 920-7.
269. Pereira BJ, Levey AS. Hepatitis C virus infection in dialysis and renal *Transplantation*. *Kidney Int* 1997; 51: 981-99.
270. Fissell RB, Bragg-Gresham JL, Woods JD, Jadoul M, Gillespie B, Hedderwick SA, Rayner HC, et al. Patterns of hepatitis C prevalence and seroconversion in hemodialysis units from three continents: the DOPPS. *Kidney Int* 2004; 65: 2335-42.
271. Jadoul M, Cornu C, van Ypersele de Strihou C. Incidence and risk factors for hepatitis C seroconversion in hemodialysis: a prospective study. The UCL Collaborative Group. *Kidney Int* 1993; 44: 1322-6.
272. Puro V, Petrosillo N, Ippolito G. Risk of hepatitis C seroconversion after occupational exposures in health care workers. Italian Study Group on Occupational Risk of HIV and Other Bloodborne Infections. *Am J Infect Control* 1995; 23: 273-7.
273. Brugnano R, Francisci D, Quintaliani G, Gaburri M, Nori G, Verdura C, Giombini L, et al. Antibodies against hepatitis C virus in hemodialysis patients in the central Italian region of Umbria: evaluation of some risk factors. *Nephron* 1992; 61: 263-5.
274. Centers for Disease C, prevention. Hepatitis C virus transmission at an outpatient hemodialysis unit- New York, 2001-2008. *Morb Mortal Wkly Rep* 2009; 58: 189-94.
275. Okuda K, Hayashi H, Kobayashi S, Irie Y. Mode of hepatitis C infection not associated with blood transfusion among chronic hemodialysis patients. *J Hepatol* 1995; 23: 28-31.
276. Gilli P, Moretti M, Soffritti S, Marchi N, Malacarne F, Bedani PL, De Paoli Vitali E, et al. Non-A, non-B hepatitis and anti-HCV antibodies in dialysis patients. *Int J Artif Organs* 1990; 13: 737-41.
277. Jadoul M, Cornu C, van Ypersele de Strihou C. Universal precautions prevent hepatitis C virus transmission: a 54 month follow-up of the Belgian Multicenter Study. The Universitaires Cliniques St-Luc (UCL) Collaborative Group. *Kidney Int* 1998; 53: 1022-5.
278. Summary of product characteristics, Victrelis 200 mg hard capsules [cited; Available from: http://www.medicines.org.uk/emc/medicine/24768/SPC/
279. Ghosal A, Yuan Y, Tong W, Su AD, Gu C, Chowdhury SK, Kishnani NS, et al. Characterization of human liver enzymes involved in the biotransformation of boceprevir, a hepatitis C virus protease inhibitor. *Drug Metab Dispos* 2011; 39: 510-21.

280. Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, Focaccia R, et al. Telaprevir is effective given every 8 or 12 hours with ribavirin and peginterferon alpha-2a or -2b to patients with chronic hepatitis C. *Gastroenterology* 2011; 140: 459-468 e1; quiz e14.
281. Buti M, Agarwal K, Horsmans Y. OPTIMIZE trial: non-inferiority of twice-daily telaprevir versus administration every 8 hours in treatment-naive, genotype 1 HCV infected patients. *Hepatology* 2012; 56: 91A-144A.
282. Van Heeswijk RP1, Beumont M, Kauffman RS, Garg V. Review of drug interactions with telaprevir and antiretrovirals. *Antivir Ther* 2013; 18: 553-60.
283. Garg V, Chandorkar G, Farmer HF, Smith F, Alves K, van Heeswijk RP. Effect of telaprevir on the pharmacokinetics of midazolam and digoxin. *J Clin Pharmacol* 2012; 52: 1566-73.
284. Kiser JJ, Burton JR, Jr., Everson GT. Drug-drug interactions during antiviral therapy for chronic hepatitis C. *Nat Rev Gastroenterol Hepatol* 2013; 10: 596-606.
285. VICTRELIS capsules, prescribing information [cited; Available from: http://www.merck.com/product/usa/pi_circulars/v/victrelis/victrelis_pi.pdf2013
286. Summary of product characteristics, INCIVO 375 mg film coated tablets [cited; Available from: http://www.medicines.org.uk/EMC/medicine/25038/SPC/INCIVO+375+mg+film+coated+tablets/2012.
287. Back D, Else L. The importance of drug-drug interactions in the DAA era. *Dig Liver Dis* 2013; 45 (Suppl 5): S343-8.
288. Hulskotte EG, Feng HP, Xuan F, van Zutven MG, Treitel MA, Hughes EA, O'Mara E, et al. Pharmacokinetic interaction between the hepatitis C virus protease inhibitor boceprevir and cyclosporine and tacrolimus in healthy volunteers. *Hepatology* 2012; 56: 1622-30.
289. Garg V, Kauffman RS, Beaumont M, van Heeswijk RP. Telaprevir: pharmacokinetics and drug interactions. *Antivir Ther* 2012; 17: 1211-21.
290. Lee JE, van Heeswijk R, Alves K, Smith F, Garg V. Effect of the hepatitis C virus protease inhibitor telaprevir on the pharmacokinetics of amlodipine and atorvastatin. *Antimicrob Agents Chemother* 2011; 55: 4569-74.
291. Hulskotte E, Gupta S, Xuan Y. Pharmoacokinetic evaluation of the interaction between the HCV protease inhibitor and the HMG-CoA reductase inhibitors atorvastatin and pravastatin, 16th Annual Meeting of HEP DART; 2011.
292. Zinego AL, Craxi A. Extrahepatic manifestations of hepatitis C virus infection. *Clin Liver Dis* 2008; 12: 611-36.
293. Ko HM, Hernandez-Prera JC, Zhu H, et al. Morphologic features of extrahepatic manifestation of hepatitis C virus infection. Clin Develop Immunes 2012; 740138: 1-9.
294. Iannuzzella F, Vaglio A, Garini G. Management of hepatitis C virus related mixed cryoglobulinemia. *Am J Med* 2010; 123: 400-8.
295. Saadoun D, Delluc A, Piette JC, Cacoub P. Treatment of hepatitis C-associated mixed cryoglobulinemia vasculitis. *Curr Op Rheumatol* 2008; 20(1): 23-8.
296. Ghosn SH, Kibbi AG. Cutaneous manifestations of liver diseases. *Clin Dermatology* 2008; 26: 274-82.
297. Fabrizi F, Lunghi G, Messa P. Therapy of hepatitis C virus-associated glomerulonephritis: current approaches. *J Nephrol* 2008: 21: 813-25.
298. Biasiotta A, Casato M, La Cesa S, Colantuono S, Di Stefano G, Leone C, Carlesimo M, et al. Clinical, neurophysiological, and skin biopsy findings in peripheral neuropathy associated with hepatitis C virus-related cryoglobulinemia. *J Neurol* 2014; 261: 725-31.
299. Caballes FR, Sendi H, Bonkovsky HL. Hepatitis C, porphyria cutanea tarda and liver iron: an update. *Liver Int*ernational 2012, 32 (6): 880-93.
300. Jadali Z. Dermatologic manifestations of hepatitis C infection and the effect of interferon therapy: a literature review. *Arch Iran Med* 2012; 15(1): 43-8.
301. Cunha KS, Manso AC, Cardoso AS, Paixão JB, Coelho HS, Torres SR. Prevalence of oral lichen planus in Brazilian patients with HCV infection. *Oral Surg Med Pathol Radiol Endodontol* 2005; 100(3): 330-3.
302. Calvaruso V, Craxi A. Immunological alterations in hepatitis C virus infection. World *J Gastroenterol* 2013; 19(47): 8916-23.
303. Zignego AL, Piluso A, Gianinni C. HBV and HCV chronic infection: autoimmune manifestations and lymphoproliferation. *Autoimmunity Reviews* 2008; 8: 107-11.
304. Dammacco F, Lauletta G, Montrone M, et al. Mixed cryoglobulinemia: a model of virus-related disease in internal medicine. *Dig Liver Dis* 2007, 39(suppl 1): 58-12.
305. Fabrizi F, Dixit V, Messa P. Antiviral therapy of symptomatic HCV-associated mixed cryoglobulinemia: meta-analysis of clinical studies. *J Med Virol* 2013; 85: 1019-27.
306. Saadoun D, Pereche Rigon M, Thibault V. Antiviral treatment for hepatitis C virus associated mixed cryoglobulinemia vasculitis: a long term follow up study. *Arthr Rheum* 2006; 54: 3696-706.
307. Saadoun D, Resche Rigon M, Thibault V, Longuet M, Pol S, Blanc F, Pialoux G, et al. Peg-IFNα/ribavirin/protease inhibitor combination in hepatitis C virus associated mixed cryoglobulinemia vasculitis: results at week 24. *Ann Rheum Dis* 2014; 73: 831-7.
308. Cacoub P, Delluc A, Saadoun D, Landau DA, Sene D. Anti-CD20 monoclonal antibody (rituximab) treatment for cryoglobulinemic vasculitis: where do we stand? *Ann Rheum Dis* 2008; 67(3): 283-7.
309. Visentini M, Ludovisi S, Petrarca A, Pulvirenti F, Zaramella M, Monti M, Conti V, et al. A phase II single arm multicenter study of low dose rituximab in patients with hepatitis Cvirus-related mixed cryoglobulinemia and severe liver disease. *Autoimmun Rev* 2011; 10 (11): 714-9.
310. Petrarca A, Rigacci L, Caini P, Colagrande S, Romagnoli P, Vizzutti F, Arena U, et al. Safety and efficacy of rituximab in patients with hepatitis c virus-related mixed cryoglobulinemia and severe liver disease. *Blood* 2010; 116(3): 335-42.
311. Dammacco F, Tucci FA, Lauletta G, Gatti P, De Re V, Conteduca V, Sansonno S, et al. Pegylated interferon-α, ribavirin, and rituximab combined therapy of hepatitis C virus-related mixed cryoglobulinemia: a long-term study. *Blood* 2010; 116: 343-53.
312. Saadoun D, Resche Rigon M, Sene D, Terrier B, Karras A, Perard L, Schoindre Y, et al. Rituximab plus Peg-interferon-α/ribavirin compared with Peg-interferon-α/ribavirin in hepatitis C-related mixed cryoglobulinemia. *Blood* 2010; 116: 326-34.
313. Cacoub P, Terrier B, Saadoun D. Hepatitis C virus mixed cryoglobulinemia vasculitis: therapy options. *Pres Med* 2013; 84(4): 523-7.
314. Terrier B, Cacoub P. Cryoglobulinemia vasculitis: an update. *Curr Op Rheumatol* 2013; 25: 10-84.
315. Terrier B, Semoun O, Saadoun D, Sène D, Resche-Rigon M, Cacoub P. Prognostic factors in patients with hepatitis C virus infection and systemic vasculitis. *Arthritis Rheum* 2011; 63(6): 1748-57.