

SASLT Practice Guidelines: Management of Hepatitis C Virus Infection

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This guideline has been approved by the Saudi Association for the Study of Liver diseases and Transplantation and represents the position of the Association.

These practice guidelines have been written to assist physicians and other health care providers to aid in the recognition, diagnosis, and management of chronically infected hepatitis C virus (HCV) patients. They are based on a formal review and analysis of published literature on the topic that impact the management of chronic HCV infection, and the experience of the authors in hepatitis C. In addition, various international practice guidelines and consensus documents on management of chronic hepatitis C were considered in the development of these guidelines. The recommendations contained herein suggest preferred approaches to the diagnostic, therapeutic, and preventive aspects of care related to the disease.

Our understanding of the natural history of HCV infection and the potential for therapy of the resultant disease is continuously improving. However, despite the increasing

knowledge, areas of uncertainty still exist and therefore clinicians, patients, and public health authorities must continue to make choices on the basis of the evolving evidence. Therefore, these guidelines are intended to be flexible and may be updated periodically as new information becomes available.

MATERIALS AND METHODS

The Saudi Association for the Study of Liver diseases and Transplantation (SASLT) formed a task force to evaluate the current epidemiology, trends in, and management of the hepatitis C virus (HCV) infection in Saudi Arabia. A majority of the members of the committee were hepatologists.

The first step was a broad literature search of published literature on every aspect of the epidemiology, natural history, risk factors, diagnosis and management of HCV. All available literature on the topic was examined critically, and the available evidence was then classified according to its importance.

The contents of the resulting document, including the recommendations contained in it, have been discussed in detail and agreed upon by members of the SASLT task force. The document was also reviewed by a content expert from another country and valuable additional input was incorporated. Subsequently, and after review by the board of directors, the guidelines were approved and endorsed by SASLT.

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All recommendations in these guidelines are based on the best available evidence, and tailored to patients treated in Saudi Arabia. They are graded on the basis of evidence.

The purpose of these guidelines is to improve HCV patient care in the Kingdom, and to promote and improve the multidisciplinary care required in the treatment of these patients. They are intended for use by physicians, and also offer recommended approaches to the diagnosis, treatment and prevention of HCV.

Grading of recommendations

Grade A

Recommendation based on at least one high quality randomized controlled trial or at least one high quality meta-analysis of methodologically sound randomized controlled trial.

Grade B

Recommendation based on high quality case-control or cohort studies or a high quality systematic review.

Grade C

Recommendation based on non-analytic studies (case reports or case series).

Grade D

Recommendation based on expert opinion only.

GOALS OF THESE GUIDELINES

These are as follows:

1. To provide a concise, evidence-based review of the diagnosis and management of chronic HCV infection in Saudi Arabia.
2. To help initiate plans to prevent HCV infection in the population.
3. To achieve early and accurate diagnosis of patients with HCV infection.
4. To provide an evidence-based approach for the management of HCV-infected patients.
5. To facilitate appropriate and timely referrals between primary, secondary, and tertiary care providers.
6. To identify gaps in the knowledge and understanding of the incidence of HCV in Saudi Arabia that require further research.

EPIDEMIOLOGY

Prevalence and incidence

HCV infection is a leading cause of cirrhosis, liver failure and liver cancer worldwide, making it a major public health issue. The World Health Organization (WHO) estimates a worldwide prevalence of 3%. Each year, three to four million people are newly diagnosed with HCV, and it remains

endemic in many countries of the world.^[1-3] According to the WHO, there are at least 21.3 million HCV carriers in Eastern Mediterranean countries, a figure close to the combined number of estimated carriers in the Americas and Europe.

A large, cross-community, population-based survey from different regions of Saudi Arabia was performed among children aged 1-10 to estimate the prevalence of HCV in Saudi children. Out of 4,496 children, 39 (0.90%) tested positive for HCV antibodies. However, the survey was performed using a first generation Enzyme-linked Immunosorbent Assay (ELISA) kit that is known to produce false-positives.^[4]

As a part of a hepatitis B virus (HBV) vaccination follow-up study, children were also tested for HCV serology using a more reliable third generation ELISA test coupled with a Recombinant Immunoblot Assay (RIBA) for confirmation.^[5] This study showed the prevalence of HCV antibodies to be higher in adolescents than in younger children: from 0.04% in 1997 (children aged 1-12 years), to 0.22% for adolescents aged 16-18 years in 2008 (unpublished results), a trend possibly related to different exposures to risk in different age groups. This increasing prevalence with age was also reported by Fakeeh *et al.*: 4.49% in < 15 years olds, 2.05% in 15-21 year olds, 5.10% in 25-34 year olds, 8.64% in 35-44 year olds, 15.0% in 45-54 year olds, and 11.9% in ≥ 55 year olds in a cohort of outpatient's attendees and hospital-admitted patients.^[6] However, these seemingly high rates are not generalizable as the patient population was not representative of the country in general. The Saudi Ministry of Health (MOH) report found a much higher proportion of HCV infection in adults (23,950/11,878,260) when compared to patients younger than 15 years old (998/8,186,369), despite similar mean population sizes. Memish *et al.*, reported an almost 45-fold higher annual incidence of seropositivity in those ≥ 15 years vs. children < 15 years of age.^[7]

The prevalence in the general population is generally considered uncertain, since most studies were conducted more than 10 years ago.^[6,8-10] HCV has been reported to be on the decline over the past decade, although it remains a major public health concern in the country.

While HCV infection has been a reportable disease in Saudi Arabia since 1990, the level of reporting compliance is unknown, hence epidemiologic estimates may be inaccurate. However, blood donors are screened, and pre-marital testing for HCV infection has been mandatory since January 2008. It is estimated that well over one million individuals have already been screened. Nested data, not confirmed by PCR-based testing, reported from the General Directorate for Communicable Diseases, Riyadh region, revealed a HCV sero-prevalence of 0.33%.^[11] A large community-based study reporting the actual prevalence of HCV in Saudi Arabia

has not yet been undertaken. However, a summary report compiled by the WHO mentions 437,292 official reports of HCV infections among persons living in Saudi Arabia, giving an estimated prevalence of about 1.8%.^[12] A study by the Saudi MOH of all of all reported cases in Saudi Arabia from January 1995 to December 2005 showed considerable differences in the number of cases reported to the MOH per region. The highest prevalence occurred in Al Baha and Jeddah (0.32%), and the lowest in Jizan (0.016%) and estimated the prevalence rate among children < 15 years to be 0.012% and that among adults to be 0.202%.^[13] These results are mirrored by earlier studies undertaken in the country. For example, blood screening results taken from 528 blood donors in the Jeddah region reported a prevalence of 1.7% infection, whereas another study of 557,815 Saudi adult residents in the Riyadh province found 1.1% anti-HCV prevalence.^[14,15]

A recent viral hepatitis surveillance study reported an annual average incidence of seropositivity of 78.4 per 100,000 of the population served by the National Guard Health Affairs (NGHA) hospitals in the Central, Eastern, and Western regions of the country.^[7] HCV incidence decreased by 30% over the eight-year study period. Prevalence rates from Saudi blood donor screening centres range from 0.4-1.1%.^[16-18]

Gender has not emerged as a sizeable factor in HCV infections in Saudi Arabia. Only one study found a higher prevalence of HCV among men compared with women, though the significantly higher age of the men could have contributed to this difference.^[6] On the other hand, a community-based study of equal numbers of men and women did not find any gender differences in infection rates.^[8] A retrospective study in the Eastern Province did not find any significant differences in HCV infection between men and women either.^[19] In two further separate reports, the prevalence of HCV infection was not shown to differ between men and women.^[7,20]

A recent systematic review of studies published in indexed sources, as well as from non-indexed sources, such as the MOH website, estimated that the prevalence of HCV in Saudi Arabia was at 1-1.9% among adults.^[21]

Genotypes

In Saudi Arabia, genotype 4 HCV is most prevalent, followed by genotype 1. In the largest genotype study on 1013 Saudi nationals, HCV G1 accounts for 25.9%, G2 for 4.3%, G3 for 2.9%, G4 for 60%, G5/G6 for 0.3% and 6.3% were of mixed genotype. In addition, 81.1% of all HCV patients are older than 41 years of age, and males account for 55.3% in G1, and 44.9% in G4 cases.^[21] (I. Altraif *et al.*, unpublished data).

Genotypes 2a/2b has been documented in the eastern region and genotype 5 in the western region of the country, with genotypes 3 and 6 being extremely rare.^[6,14,22-25] The most

common subtypes of genotype 4 HCV among Saudis are 4c/4d followed by subtypes 4h, 4e, and 4a.^[14,26]

Risk factors

The primary source of HCV transmission is parenteral exposure to HCV-infected blood or blood products.

Hemodialysis

Patients on hemodialysis are particularly at risk of contracting HCV. In Saudi Arabia, hemodialysis is the most commonly used form of renal replacement therapy, and the number of patients receiving hemodialysis treatment has been increasing dramatically.^[17,18,27] At the same time, the incidence of new infection, and the prevalence of HCV has increased in this patient population over the past three decades, and it is now estimated to be 7-9% and 15-80%, respectively.^[17] Additionally, there was a surge in endemicity in the mid-1990s, from 41% to 55%, appearing simultaneously with the sudden expansion of hemodialysis services, due to a significant increase in the number of patients with end-stage renal disease across the country.^[17,27]

In recent years, based on more available data, and countrywide figures from the Saudi Centre for Organ Transplant, the HCV prevalence rate has remained constant at 50%, even though the demand for dialysis services continues to rise, perhaps as a reflection of better adherence to infection prevention and control policies and practices.^[17,27] In fact, a recent single-centre study that adopted strict infection control guidelines reported a zero incidence of infection for the entire duration of 5 years that 36 sero-negative hemodialysis patients were followed.^[28] Another investigational study followed the epidemiology of HCV in a dialysis unit after methods to reduce prevalence of the virus were set in place.^[29] These practices included strict adherence to universal infection control precautions, separation of HCV-positive patients from the negative ones, and using specially designated machines for the HCV-negative hemodialysis patients. Periodic testing revealed no sero-conversions and a reduced prevalence of HCV RNA-positive patients to 6.5% within the unit.

A study by Abu-Aisha *et al.* recommended the delegation of specific hemodialysis machines for anti-HCV-positive cases.^[30] Soyannwo *et al.* also determined that machine isolation policies, rather than blood transfusions, lead to wide-spread variations in the prevalence of HCV among different dialysis centres in Saudi Arabia.^[31] Several studies have also referred to patient isolation as an important factor in preventing transmission of viral hepatitis in hemodialysis units.^[32-34] For instance, a specially designed centre with complete isolation of HCV-negative and HCV-positive patients resulted in the annual incidence of HCV infection dropping significantly from 2.4% to 0.2%.^[34]

Intravenous drug users

Acquisition of Hepatitis C by intravenous drug users constitutes only a small percentage of the total HCV infection cases in Saudi Arabia, despite the continued rise in number of IV drug users.^[13,35] Recent examination of the prevalence of viral infection among 344 Saudi injecting drug users reported a 38% HCV RNA detection rate with a predominant genotype of 1b.^[35] An earlier study showed that the HCV infection among IV drug users in a Jeddah detoxification center was 69%.^[36]

Other risk factors

Additional potential risk factors for HCV transmission include exposure to an infected sexual partner, or multiple sexual partners, and perinatal exposure.^[37] Few studies have been done on these topics, and the available data are conflicting. One study concluded that intrafamilial transmission was a major route of transmission among the Saudi population,^[38] while two others showed that neither intrafamilial^[39] nor perinatal^[13] transmission are risk factors for HCV infection in Saudi Arabia. Further studies need to be undertaken to explore modes of transmission of HCV in the local population.

Other forms of transmission such as bloodletting and traditional tattooing have been suggested.^[40] In addition, a study by Al Faleh *et al.*, has documented a history of prior blood transfusion in 14.8% of infected patients.^[14] The low prevalence of HIV in the Saudi population relegates it as a risk factor of marginal importance in the local setting.^[18,41,42] Other high risk group patients such as patients with thalassemia major and hemophilia have a prevalence rate of 70% and 78.6%, respectively.^[10,41] A prevalence of 15.9% has been reported in patients with sexually-transmitted diseases^[42] and high risk behavior.

Recommendations

1. HCV testing is recommended for (Grade B)
 - a. Individuals with a history of intravenous drug use.
 - b. Patients with conditions associated with a high prevalence of HCV infection, including those.
 - With HIV infection
 - With hemophilia, who received clotting factor concentrates before 1987
 - Who ever underwent hemodialysis
 - With unexplained abnormal aminotransferase levels
 - c. Prior recipients of transfusions or organ transplants, including those.
 - Who were notified that they had received blood from a donor who later tested positive for HCV infection
 - Who received a transfusion of blood or blood products before July 1992
 - Who underwent an organ transplant before July 1992

- d. Children born to HCV-infected mothers.
 - e. Health care, emergency medical and public safety workers after a needle stick injury or mucosal exposure to HCV-positive blood.
 - f. Sexual partners of HCV-infected persons.
2. Individuals found to have HCV infection should be counseled regarding prevention of the spread of the virus to others. They should be informed that transmission occurs through contact with their blood, and they should therefore be informed about how to take precautions against the possibility of such exposure (Grade B).^[43]

NATURAL HISTORY

The HCV is one of the most important Flaviviridae infections in humans, and is the second most common cause of viral hepatitis.^[44] HCV has six major genotypes, which are indicated numerically (1 to 6) according to the international Simmonds classification.^[45]

HCV infection can present as an acute hepatitis, chronic hepatitis, extra-hepatic manifestation, or as cirrhosis and its complications. Acute hepatitis is usually asymptomatic, not commonly encountered in general clinical practice and rarely leads to hepatic failure. Natural history studies suggest that 55-85% of persons with acute hepatitis C will go on to develop chronic HCV infection, while the remaining 15-45% of patients with acute hepatitis C will spontaneously clear the virus without developing any long-term complications and require no further treatment. Those having persistent infection for more than six months are defined as chronic hepatitis C.^[46] Of these, 5-20% have been reported to develop cirrhosis over a period of 20 to 25 years.^[47-49] The high figure of 20% of chronic HCV patients developing cirrhosis may not reflect the true rate in the general population of HCV-infected persons, since these studies were done in tertiary-care hospitals and may have had referral bias. A very small portion of chronic HCV patients (0.5% to 0.74% per year) spontaneously clear their virus.^[50] Patients with HCV-induced cirrhosis have a risk of about 30% over 10 years for developing end-stage liver disease, and about 1-4% risk per year for developing hepatocellular carcinoma (HCC).^[51,52]

The 10-year risk of cirrhosis is less than 10% in patients with mild chronic hepatitis, 44% in those with moderate hepatitis, and 100% in those with severe hepatitis with bridging fibrosis.^[53]

Evolution of chronic HCV infection to cirrhosis is a primary concern. Factors that accelerate the rate of progression include excessive alcohol intake, existing HIV and/or HBV, a longer duration of HCV infection, males, and those patients acquiring the infection when under the age of 40, or who acquire it through blood transfusion rather than

through drug use by injection.^[53-58] An important predictor of the future progression of liver disease and the need for HCV treatment is more-than-portal fibrosis on liver biopsy (Metavir ≥ 2 or Ishak ≥ 3).^[55,59,60]

Due to the long course of hepatitis C, the exact risk of cirrhosis is very difficult to determine, and figures differ from study to study and between populations. Data from Egypt has suggested a possible relationship between HCV genotype 4 and HCC, where the vast majority of patients have genotype 4.^[61-66] Such data is not available in Saudi Arabia and its relevance in the local setting needs to be further explored. The Saudi Observatory Liver Disease (SOLID) registry has recently been established through a national funding initiative termed as the National Plan for Science and Technology, under the auspices of King Abdulaziz City for Science and Technology in Riyadh. The SOLID registry functions on a nationwide basis, with a constantly expanding list of participating centers. The registry aims to prospectively accrue demographic, clinical and treatment-related data in patients with HCV and other liver diseases. It is at present the only longitudinal, hospital-based, research database in the region.

Deaths related to chronic HCV are usually caused by complications of decompensated cirrhosis and HCC. The onset of decompensation is associated with a rapid decline in survival rates. The 5-year survival rate for patients with compensated cirrhosis is as high as 90%, compared to 50% for those with decompensated cirrhosis.^[67-69]

CLINICAL FEATURES OF HCV INFECTION

Infection with HCV can result in both acute and chronic hepatitis, each with a different spectrum of clinical manifestations.

Acute HCV

Acute HCV infection is usually asymptomatic. However, approximately 25% of patients with acute HCV present with jaundice, and less than 33% develop non-specific symptoms such as nausea, vomiting, abdominal pain, and fatigue or arthralgia. Less common symptoms include fever and rash. In patients who experience the symptoms of acute hepatitis, the illness typically lasts for 2-12 weeks. The incubation period from infection to onset of symptoms can range from 2 to 12 weeks.^[70,71]

HCV RNA typically becomes detectable in serum 7 to 21 days after exposure, and can be detected at high levels at the onset of jaundice.^[71]

Aminotransferase levels become elevated approximately 6-12 weeks after exposure, and can be more than 15 times the upper limit of normal.^[72]

Anti-HCV becomes detectable approximately 7-10 weeks after the onset of infection.

Fulminant hepatic failure due to acute HCV infection is very rare. It may be more common in patients with underlying chronic hepatitis B virus infection.^[73]

Chronic HCV

In chronic hepatitis C, the disease may continue to appear to resolve both biochemically and histologically, followed by intermittent or constant elevation of serum transaminases. Most patients with chronic infection are asymptomatic or have only mild nonspecific symptoms, and do not have physical signs of liver disease, as long as cirrhosis itself is not present.^[74]

Extrahepatic manifestation of HCV

Patients with these syndromes can be divided into those with a higher degree of association, and those with a more moderate or mild association with HCV. The most prevalent extra-hepatic diseases with the highest degree of association with HCV are the essential mixed cryoglobulins with a clinical triad of weakness, arthralgia and palpable purpura. Renal disease can also be associated with chronic HCV, particularly membranoproliferative glomerulonephritis.^[75,76]

The other diseases include noncryoglobulinemic systemic vasculitis, splenic lymphoma with villous lymphocytes, fatigue, porphyria cutanea tarda, sicca syndrome, and autoantibodies production. The extra-hepatic manifestations that share mild-degree certainty of association with HCV infection include B-cell non-Hodgkin lymphoma, autoimmune thrombocytopenia, pruritus, and type II diabetes mellitus. The other diseases such as autoimmune thyroiditis, lichen planus are less likely to be associated with HCV.^[77,78]

Most extra-hepatic manifestations of chronic HCV infection are immunological, and a chronic level of infection seems to be necessary for their development. Molecular study of the unique way in which the HCV virus interacts with the human immune system is slowly beginning to provide plausible explanations of the pathogenic role of HCV in some of these syndromes, but many patho-genetic links remain completely obscure.^[79]

Cirrhosis and hepatocellular carcinoma

Patients with normal serum transaminases activity have a lower fibrosis progression rate (15%) than those patients with elevated enzymes.^[80]

Cirrhosis can be missed clinically, as most cirrhotic patients are asymptomatic as long as hepatic decompensation and HCC does not occur. The HCV-related compensated cirrhosis is usually discovered during screening of blood donors, premarital screening or at the time of routine laboratory testing.^[59,67]

A wide spectrum of nonspecific symptoms can be noted in patients with compensated and decompensated cirrhosis, including fatigue in 75%, abdominal pain in 24%, and anorexia in 13%.^[81]

Less than 50% of cirrhotic patients have clinical and laboratory results that support the presence of cirrhosis like hepatomegaly and/or splenomegaly, spider angiomas, palmar erythema, testicular atrophy, or gynaecomastia, caput medusa, elevated serum bilirubin concentration, hypoalbuminemia, or low platelet counts.

Among patients with compensated cirrhosis, the annual risk of decompensation is 3.9%. The clinical presentation can be dramatic after hepatic decompensation, and manifests itself with ascites in 48%, variceal bleeding in 22-32%, hepatic encephalopathy in 5-8%, jaundice in 6%, or a combination of these complications in 17% of patients. Patients with hepatic decompensation may also develop lower extremity edema, pruritus, sexual dysfunction, easy bruising, muscle wasting and muscle cramps.

Patient with HCV-related cirrhosis are at risk of HCC, and the estimated risk, described in various reports, has varied from 0-3% per year. The suspicion of HCC development should be high in those patients who present with rapid clinical decompensation with ascites, hepatic encephalopathy and bleeding from portal hypertension. Ultrasound of the abdomen at 6 months intervals is the recommended test that can be used for early detection of HCC in patients with HCV cirrhosis.^[67,82]

Recommendations

1. The Saudi Observatory Liver Disease Registry (SOLID) is a valuable source of data for HCV in Saudi Arabia, and efforts must be made to improve patient registration and the utilization of the registry (Grade D).
2. Large epidemiologic studies are needed to further define the epidemiologic features and natural history of HCV infection in Saudi Arabia (Grade D).
3. Patients with significant fibrosis caused by HCV are at significant risk for disease progression (Grade A).
4. Patients with cirrhosis caused by hepatitis C are at high risk for the development of HCC and these patients should be regularly screened to detect the onset of early HCC (Grade A).

LABORATORY TESTING

Alanine aminotransferase and aspartate aminotransferase

Liver chemistries are an insensitive means of assessing fibrosis. Elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) may indicate the presence

of liver disease, but does not determine the type, the cause of the liver disease, or correspond to the degree of damage on liver biopsy.^[83] Additionally, viral genotype and/or viral load do not correlate with the amount of liver injury.^[84] In 341 anti-HCV positive patients in the study by Silini *et al.*, 49% had persistently normal or nearly normal ALT levels and of those 70% had circulating HCV RNA; while on histology a large number of them had mild chronic hepatitis.^[85] Therefore, if there is a suspicion of HCV infection in patients with a persistently normal ALT level, they should be tested for HCV-RNA. The use of routine liver tests to screen for chronic hepatitis C virus infection is of limited value in cases of anti-HCV and PCR positives.^[86] Other studies have shown that transaminase levels can be helpful in predicting the severity of liver disease, with higher levels associated with more advanced histology, but they are usually of limited value in an individual patient.^[58,87] With levels fluctuating from normal to abnormal over time, the value of monitoring transaminases is limited. Additionally, the results of routine liver tests correlate poorly with both necro-inflammatory and fibrosis scores found on liver biopsy.

Serologic assays

Detection of the anti-HCV antibody is used for screening for HCV infection. The two enzyme immunoassays (EIAs) commonly used are Abbott HCV EIA 2.0 (Abbott Laboratories, Abbott Park, IL) and ORTHO® HCV Version 3.0 ELISA (Ortho-Clinical Diagnostics, Raritan, NJ). The enhanced chemi-luminescence immunoassay (CIA) VITROS® Anti-HCV assay, (Ortho-Clinical Diagnostics, Raritan, NJ) is also used for the same purpose. The specificity of third generation EIAs for detection of anti-HCV is greater than 99%;^[88] at the same time, they are reproducible and inexpensive.^[43] The recombinant immunoblot assay, Chiron RIBA HCV 3.0 SIA (Chiron Corporation, Emeryville, CA) is more specific, and is a supplemental assay to confirm the results of EIA testing.^[89,90] The specificity is extremely high for third generation EIA, that exceeds particular signal/ cutoff ratios (e.g., >3.8 for the above mentioned Ortho and Abbott EIA tests).^[91,92] Its high sensitivity and specificity may obviate the need for a confirmatory immunoblot assay in the patient with HCV infection. However, a positive RIBA is not diagnostic of active HCV infection, since up to 45% of patients will clear HCV spontaneously after acute infection, while remaining anti-HCV positive.^[46]

The hepatitis C virus antibodies revealed by ELISA are detectable within three to 15 weeks of infection. The third-generation anti-HCV enzyme immunoassay (EIA) can detect HCV antibodies as early as 6–8 weeks after exposure.^[93] Anti-HCV antibodies can be detected in 80% of HCV patients within 15 weeks after exposure, in > 90% within 5 months after exposure, and in > 97% up to 6 months after exposure.

Overall, HCV antibody tests have a strong positive predictive value for exposure to the hepatitis C virus.

One of the newest assays, the Murex HCV Ag/Ab combination assay combines the detection of anti-HCV antibodies with the detection of core antigen in a single assay, which significantly reduces the window period from infection to detection when compared with conventional serological HCV antibody screening assays.^[94]

Second- and third-generation tests, which have included more antigens from the better-conserved regions of the viral genome, have high sensitivity and specificity for detection for all genotypes. Use of this technique runs the risk of false-negative results of less than 5%.^[95] If a reaction with two or more of the antigens is seen, the RIBA test is considered positive.^[96] Reaction with only one antigen gives an indefinite test result; only about 10% of these patients are HCV-RNA-positive.^[97] The recombinant viral antigens from HCV are used in all commercial assays, and consequently false-negative results are less likely, due to amino-acid heterogeneity. False positive results are more likely to occur when testing is performed among populations where the prevalence of hepatitis C is low. False negative results are more likely in patients who have not yet developed antibodies (*seroconversion*), have an insufficient level of antibodies to be detected, immunocompromised individuals who may never develop antibodies to the virus, in the presence of hypo- or agammaglobulinemia, and in patients on hemodialysis.^[98-100]

Molecular assays

The presence of the virus is tested by using molecular nucleic acid testing methods, such as polymerase chain reaction (PCR), transcription mediated amplification (TMA), or branched DNA (b-DNA). All HCV nucleic acid molecular tests have the capacity to detect the presence of the virus and to measure the amount of the virus present in the blood (the HCV viral load).

Historically, qualitative assays have been shown to be more sensitive than quantitative assays. Most recently, available real-time polymerase chain reaction (PCR) has shown the ability to detect even a small amount of HCV RNA (<10 IU/ml) and to accurately quantify HCV RNA levels up to 10⁷ IU/ml. Their dynamic quantification range adequately covers clinical needs for diagnosis and monitoring.^[101-103] With transcription mediated amplification (TMA) assays, the sensitivity is up to 10-50 IU/mL.^[104] A highly sensitive assay with a lower detection limit is considered appropriate for monitoring during therapy. All available assays have excellent specificity, namely in the range of 98% to 99%.

The international standard for HCV RNA nucleic acid is well accepted for uniformity,^[44] and is now preferred over viral

copies.^[105,106] The hepatitis C virus is usually detectable in the blood by PCR within one to three weeks of infection.^[93] However, more recently HCV antigen assays (HCV core antigen) has significantly reduced the window period (i.e., period prior to the detection of an antibody).^[107-111] The assay based on the detection of the HCV core protein (Trak-C; Ortho Clinical Diagnostics) has proposed an alternative to PCR, but it suffers from lack of sensitivity.^[112]

For monitoring purposes, it is important to use the same laboratory test before and during therapy. Traditionally, qualitative tests are more sensitive, but with a lower limit of detection 5 IU/mL [Table 1].^[113]

Viral RNA testing is indicated when there is clinical suspicion of HCV, transaminase levels are high, and antibody testing is negative.^[84]

An approach based on the HCV core protein and specific anti-HCV antibody detection (Monolisa HCV Ag-Ab Ultra; Bio-Rad Laboratories, Marnes-la-Coquette, France) has recently been developed for the diagnosis of hepatitis C.^[114,115]

Reverse transcription of the viral RNA, followed by amplification of complementary DNA (RT-PCR) has a role in diagnosis, monitoring and evaluation of therapy. Its disadvantages are the risk of contamination, and false-negative results when samples are not handled correctly. Quantitative measurements have revealed that the level of viraemia correlates with the severity of disease and reacts inversely with the response to therapy. Quantification can be done by quantitative PCR assays or by branched DNA (bDNA) techniques.^[116] In PCR, sensitivity is higher, but bDNA has better reproducibility.^[116] The lower limit of detection for earlier versions of these PCR tests has been around 600 IU/mL. More recent versions are more sensitive, with a broader dynamic range from around 5-25 IU/mL to > 108 IU/mL, depending on the laboratory of origin.^[83]

Table 1: Qualitative assays for detection of HCV RNA

Assay and manufacturer	Method	Lower limit of detection IU/mL
Amplicor HCV v2.0 (Roche Molecular Systems)(For diagnosis and monitoring)	Manual RT-PCR	50
Cobas Amplicor HCV v2.0 (Roche Molecular Systems) (For diagnosis and monitoring)	Semi-automated RT-PCR	50

RT-PCR: Reverse transcription polymerase chain reaction, HCV: Hepatitis C virus

Genotype assay

HCV genotype and subtype can be determined via various methods, including direct sequence analysis, reverse hybridization, and genotype-specific real-time PCR.^[117] Genotyping is useful in epidemiological studies, selecting therapy, predicting likelihood of response to therapy and determining the optimal duration of treatment. Up to 80% of patients with HCV genotype 2 and 3 respond favorably to antiviral therapy. Several methods are available for genotyping: (a) serologically identifying the specific peptide by ELISA,^[118] (b) sequencing of PCR products, (c) use of type-specific primers and (d) restriction fragment length polymorphism. Several commercial assays are available to determine HCV genotypes, using direct sequence analysis of the 5' non-coding region. These include the Trugene 5' NC HCV Genotyping kit (Siemens Healthcare Diagnostics Division, Tarrytown, NY). A reverse hybridization analysis using genotype specific oligonucleotide probes located in the 5' non-coding region, INNO-LiPa HCV II, (Innogenetics, Ghent, Belgium), and Versant HCV Genotyping Assay 2.0 (Siemens Healthcare Diagnostics Division, Tarrytown, NY). The analysis of conserved 5' NCR allows the determination of 3 major groups, types 1, 2, and 3,^[119,120] with type specific primers,^[121] on the basis of restriction fragment length polymorphisms (RFLP's)^[122] or with sequence specific DNA probes (genotyping).^[123] Phylogenetic analysis of the NS5 region has allowed the classification of HCV into 6 major genetic types and a number of subtypes. So far, there has been no overlap in sequence variability between the different classes with nucleotide homologies of 88-100% between isolates, 74-86% between subtypes, and 56-72% between types.

Incorrect typing among the major genotypes is rare (< 3%) and mixed genotypes are known to occur, but are uncommon. Occasionally (< 5%), tested samples cannot be genotyped. This usually results from low viral levels, issues with the PCR amplification step of the assay, or extreme nucleotide variability within the HCV genome.^[124]

Noninvasive tests to assess liver fibrosis

The use of non-invasive tests to assess liver fibrosis is not yet recommended. However, various non-invasive tests are being investigated for staging the degree of liver fibrosis. These tests may be used to decide whether or not to initiate antiviral therapy, and to monitor the effects of such therapy.^[125]

Standard liver biochemical tests (liver function and coagulation studies) and radiological imaging of the liver are not sufficiently sensitive to diagnose evolving hepatic fibrosis and early stages of cirrhosis, though it may be helpful in advanced cirrhosis.^[125]

A number of studies employing a variety of indirect markers of liver fibrosis (FibroSure and FibroStat), including standard

liver chemistries, platelet count, prothrombin index, and lipoprotein A1 concentrations, have been published recently. These tests have gained acceptance in Europe as alternatives to liver biopsy.^[126,127]

The commonly used non-invasive tests are the aspartate aminotransferase (AST)-to-platelet ratio index (APRI),^[128] the Forns index,^[129] FIB-4,^[130,131] Fibroindex,^[132] FibroTest,^[133] FibroMeter,^[134] and Hepascore.^[135] The main advantage of APRI, the Forns index, and FIB-4 over other non-invasive tests is that they are based on readily available blood tests, and are easily accessible.

The Forns index is based on platelet count, gamma glutamyl transpeptidase (GGT), age, and cholesterol.^[129] Forns score = $7.811 - 3.131 \times \ln [\text{number of platelets (10}^9\text{/L)}] \times 0.781 \ln [\text{GGT (U/L)}] + 3.467 \times \ln [\text{age (years)}] - 0.014 [\text{cholesterol (mg/dl)}]$.^[133] The Forns index was found to be slightly more accurate than the aspartate aminotransferase-platelet ratio index and FIB-4 in predicting significant fibrosis and cirrhosis.^[132]

The APRI Score (AST platelets ratio index) is a serological marker alternative to liver biopsy, and it has been found to be both satisfactorily sensitive and specific.^[136] The APRI formula was proposed by Wai *et al.*^[130] and the APRI score is calculated as follows: $[(\text{AST}/\text{upper normal limit of AST}) \times 100] / \text{number of platelets (10}^9\text{/L)}$.^[137] The results obtained are then used to plot two Receiver Operating Characteristic (ROC) curves to determine the best cutoff point for advanced fibrosis (F3 and F4). A second point on the curve is established for moderate and advanced fibrosis (F 2, 3, and 4).

The FIB-4 was originally developed to predict significant fibrosis and cirrhosis among human immunodeficiency virus (HIV)/HCV co-infected patients in the APRICOT study.^[131] The FIB-4 formula includes the alanine aminotransferase (ALT) level, the aspartate aminotransferase (AST) level, platelet count and age: $\text{FIB-4 score} = [\text{age (years)} \times \text{AST (U/L)}] / (\text{number of platelets (10}^9\text{/L)} \times \text{ALT (U/L)}^{1/2})$,^[130,131] and appears to be a strong predictor of de-compensated cirrhosis or death.^[137] In fact, both FIB-4 and APRI have been shown to have the highest positive predictive value only in cases with the most severe stages of liver fibrosis (LF).^[138] For these reasons, rather than using FIB-4 and APRI as substitutes for liver histology at a single time-point for comparison of LF among different individuals, these markers can be used to determine associated risk factors for possible LF progression.^[139] In a study by Güzelbulut *et al.*, the Forns index, APRI and FIB-4 were all found to be accurate noninvasive blood tests for the prediction of the presence or absence of significant fibrosis and cirrhosis in half of the patients studied. Although they all demonstrated

similar levels of accuracy, the Forns index performed slightly better than the APRI and the FIB-4 both in the prediction of significant fibrosis and cirrhosis. The main advantage of these tests is that they are easily reproducible, with readily available blood tests. Consequently, the use of a combination of some or all of these tests may circumvent the need for liver biopsy.^[140]

FibroTest/ActiTest

FibroTest/ActiTest estimates liver fibrosis and necrotic inflammation. These tests are validated,^[141] and recommended in Europe. ActiTest is a modification of the FibroTest that incorporates ALT, and measures both necro-inflammatory activity, and liver fibrosis of viral origin (HBV and HCV).^[142] The diagnostic value of FibroTest/ActiTest is the same for the intermediate and extreme grades of liver fibrosis. The diagnostic value is independent of ethnic origin, sex, genotype, viral load, or presence of co-morbidities. ActiTest is validated for the initial diagnosis, monitoring both treated and untreated patients.

The ActiTest result is presented as a score of 0 to 1, proportional to the significance of the activity, with a conversion to the METAVIR system (from A0 to A3). To facilitate the visual interpretation, the result is accompanied by a colored graph showing the level of severity as follows:

- Green (minimal or absent)
- Orange (moderate)
- Red (significant)

The use of FibroTest has been validated for the diagnosis of fibrosis in both treated and untreated patients. In 2006, the French National Authority for Health (HAS) recommended the use of FibroTest as a first-line assessment tool for fibrosis in patients with untreated chronic hepatitis C.

When serological markers and transient elastography are used alone or together, the results obtained are comparable to those of the liver biopsy itself.^[142,143] The use of biochemical markers of liver fibrosis (FibroTest) and necrosis (ActiTest) can be recommended as an alternative to liver biopsy for the assessment of liver injury in patients with chronic hepatitis C and both have been shown to accurately identify patients with mild fibrosis or cirrhosis. However, they have been shown to be less effective in discriminating moderate and severe fibrosis.^[126]

Histology

Liver biopsy still remains the only gold standard test for evaluating stages of fibrosis, and, when combined with clinical and laboratory findings, is also a reliable means of assessing prognosis, thus helping to provide information about the need to initiate therapy. Currently, the American Association for the Study of Liver Disease (AASLD) recommends that,

regardless of the level of ALT, a liver biopsy is advised for patients with genotypes 1 and 4. However, biopsy is not mandatory in order to initiate therapy.^[45] Histology outcomes can vary from showing only mild changes to those of chronic active hepatitis and cirrhosis,^[144] depending on the duration and severity of the disease. Histological changes indicative of chronic HCV disease are lymphoid aggregates in portal and bile duct areas, together with steatosis of hepatocytes. A combination of at least two of these features is seen in about 70% of all cases. Immunohistochemical techniques can detect HCV proteins in liver biopsy, and HCV-RNA can be detected with *in situ* PCR or bDNA techniques.

For evaluation of histo-pathological abnormalities and progression, quantitative scores have been developed for estimating the degrees of inflammation (grading) and of fibrosis (staging). The 'histological activity index' (HAI) of Knodell^[145] is widely used, but has some drawbacks. Several adaptations have been proposed, (e.g., Scheuer^[146]), mainly to separate inflammation from fibrosis scores, as each of these parameters has a distinct value for the prognosis of the disease and for evaluating the effect of therapy.

METAVIR score stage assessment for fibrosis classification in chronic hepatitis C

The scores are as follows:

- F0: No fibrosis
- F1: Portal and periportal fibrosis with no septum
- F2: Portal and periportal fibrosis with rare septum
- F3: Portal and periportal fibrosis with many septa
- F4: Cirrhosis

Necroinflammatory activity

The activity (or grade) estimates the lesions by measuring portal inflammation and hepatocellular necrosis.

METAVIR score assesses grading for activity as follows:

- A0: No activity
- A1: Minimal activity
- A2: Moderate activity
- A3: Severe activity

Recommendations

Conditions for these recommendations are:

1. Clinical signs and symptoms of chronic HCV are nonspecific, the liver chemistry and radiographic findings poorly corroborate with the activity and extent of the damage to the liver in early and late stages of the HCV infection. Diagnosis of HCV infection is based on detection of anti-HCV antibodies by enzyme immunoassay and HCV RNA by a sensitive molecular method (lower limit of detection <50 IU/ml), ideally a real-time PCR assay. The diagnosis of chronic hepatitis C is based on the detection of HCV infection (positive

- anti-HCV antibodies and HCV RNA) in a patient with signs of chronic hepatitis. Rarely, in profoundly immunosuppressed patients, anti-HCV antibodies may not be detected, but HCV RNA is always present.
- Patients with suspected HCV infection should be tested for anti-HCV by an up-to-date (currently, third generation) ELISA test (Grade B).
 - Immunosuppressed patients may require a test for HCV RNA, if hepatitis is present, but anti-HCV antibodies are undetectable (Grade B).
 - The measurement of HCV RNA concentrations in serum and identifying the HCV genotype are recommended and should be used to determine the duration of treatment (Grade A).
 - Liver fibrosis can be broadly established by means of either biochemical or hematological tests like ALT, AST, prothrombin time, platelets, APRI, AST/ALT ratio, Forns Index; those that include specific indirect markers of liver fibrosis, such as α -2macroglobulin; those that incorporate only direct markers of liver fibrosis (MP3), or combinations of direct and indirect markers (Hepascore, FibroMeter). Sufficient evidence exists to support the view that algorithms perform well in the detection of significant fibrosis (METAVIR score F2-F4). Thus, their use in patients with chronic hepatitis C can be recommended for this purpose (Grade A).
 - Liver biopsy is valuable for assessing the status and level of liver inflammation, the potential progression of fibrosis and the presence or absence of cirrhosis. It is not mandatory, and should only be considered in patients who are hesitant about HCV treatment, in order to make decisions regarding urgency of treatment. Standard histological scoring systems by a suitably experienced pathologist should be used to encourage uniformity of histological reports. In addition, the risks and benefits of liver biopsies should first be carefully explained to the patient (Grade B).

TREATMENT OF CHRONIC HCV PATIENTS

Since interferon-alpha (IFN- α) was first introduced for treatment of non-A and non-B hepatitis 2 decades ago, therapy for chronic carriers of the hepatitis C virus has improved dramatically. Historically, standard IFN monotherapy will lead to a sustained virological response (SVR) in less than 15% of patients. With the addition of ribavirin (RBV), and later the substitution of pegylated IFN-alpha (peg-IFN- α) for the standard IFN, the SVR rate significantly improved. Treatment with combined peg-IFN and RBV may result in SVR in 42% to 52% of genotype 1 infected patients, 70% to 80% of genotype 2 or 3 infected patients and 54-68% of genotype 4 infected patients.

The use of combinations of peg-IFN and RBV are thus

considered the current standard of care for the treatment of chronic hepatitis C (CHC). The purpose of anti-HCV therapy is the eradication of HCV infection, in order to prevent the occurrence of complications and death. All HCV patients with compensated chronic liver disease who have had no previous treatment for HCV, are willing to be treated, and have no contra-indication to peg-IFN- α or RBV should be considered for treatment, regardless of their baseline ALT level.

Pre-treatment predictors of response are useful for advising patients on their chance of viral eradication. Positive pre-treatment predictors of response to peg-IFN and RBV include the HCV genotypes 2 and 3, low baseline HCV RNA levels (genotypes 1 and 4 < 600,000 IU/mL, genotypes 2 and 3 < 400,000 IU/mL), IL-28B polymorphism CC type, absence of bridging fibrosis or cirrhosis, younger age (< 40 years), and those with a body mass index of < 30 Kg/m². Negative pre-treatment predictors include advanced hepatic fibrosis, HIV co-infection, and the presence of insulin resistance with or without diabetes, obesity, non-viral hepatic steatosis and possibly low vitamin D levels.^[147,148]

Table 2 summarizes the various definitions of virological responses obtained during dual antiviral therapy with peg-IFN and RBV.

Indications and contraindications of antiviral therapy

Treatment with peg-IFN- α and RBV is cost effective, even for patients showing early stages of liver fibrosis.^[149,150] A reasonable candidate for HCV therapy is an adult patient who is 18 years old or older, has HCV viremia, and displays evidence of chronic hepatitis with at least F2 fibrosis, or a well-compensated cirrhosis (total serum bilirubin < 25 μ mol/l; INR < 1.5; serum albumin > 34 g/L, no hepatic encephalopathy or ascites). Candidates should also have good hematological indices before starting antiviral therapy. Preferable pre-treatment hematological indices should be the following: hemoglobin level above 12 g/dl; neutrophil count above 1500 /mm³ and platelet count above 75,000 mm. Absolute contraindications to the use of peg-IFN- α and RBV include uncontrolled autoimmune diseases, co-morbid conditions that markedly limit life expectancy, history of hypersensitivity to peg-IFN or RBV, pregnancy, or unwillingness to use birth control during and for six months after treatment, severe cardiac disease, severe pulmonary disease, uncontrolled psychiatric conditions, and uncontrolled seizure disorders. Certain patient groups such as HIV/HCV co-infection and liver transplant patients with HCV infection should be treated at tertiary hospitals with facilities for HIV care, or liver transplant programs, respectively.

Table 2: Virological response obtained during dual antiviral therapy with pegylated interferon and ribavirin

Term	Week of therapy where definition applies	Definition
Rapid virological response (RVR)	Week- 4	Undetectable HCV RNA
Partial early virological response (pEVR)	Week- 12	Decline in HCV RNA by ≥ 2 logs from baseline
Complete early virological response (cEVR)	Week -12	Undetectable HCV RNA
Delayed virological response (DVR)	Week- 24	Undetectable HCV RNA at week 24 in patients who have partial early virological response
End of treatment response (ETR)	Week- 48 (genotype 1 and 4-6) Week 24 (genotype 2 and 3)	Undetectable HCV RNA
Treatment outcome		
Sustained virological response (SVR)	24 weeks after completing treatment	Undetectable HCV RNA
Treatment failure		
a. Null virological response	Week- 12	Decline in HCV RNA by < 2 logs from baseline (Stop Therapy)
b. Partial virological response	Week- 24	Detectable HCV RNA (≥ 50 IU/ml) at week 24 in patients who have partial early virological response (Stop Therapy)
c. Breakthrough	Any time on-treatment	Detectable HCV RNA in patient who had previously undetectable HCV RNA
d. Relapse	24 weeks after completing treatment	Detectable HCV RNA in patient who had undetectable HCV RNA, after therapy is discontinued

Recommendations

1. Eradication of HCV infection is the primary purpose of antiviral therapy (Grade A).
2. Patients with chronic HCV infection who have had no prior therapy and have compensated liver disease should be evaluated and considered for anti-HCV therapy (Grade B).

Treatment regimen and antiviral side effects

Two pegylated IFN- α are available in Saudi Arabia, namely, peginterferon alfa-2b (PegIntron[®]), with a 12-kd linear polyethylene glycol (PEG) covalently linked to the standard interferon alfa-2b molecule, and peginterferon alfa-2a (Pegasys[®]) with a 40-kd branched PEG covalently linked to the standard interferon alfa-2a molecule.^[151]

In the Individualized Dosing Efficacy versus Fixed Dosing to Assess Optimal Peg-IFN Therapy (IDEAL) trial, 3070 genotype 1 infected patients were randomized to one of the two-pegylated IFN, and no difference in SVR was obtained between the two formulations. The rate of SVR was 40.9% with peg-IFN- $\alpha 2a$ (Pegasys[®]) and 39.8% with peg-IFN- $\alpha 2b$ (PegIntron[®]).^[152] The preference as to which of them to use will therefore depend on their availability at a particular hospital or patient preference.

Ribavirin (a guanosine nucleoside analogue) is an important component of HCV dual and triple (direct-acting antiviral agents) therapy. It improves viral clearance, decreases relapse rates, and improves rates of SVR when used in combination with peginterferon, as compared with peginterferon monotherapy.

When a patient is being evaluated for HCV therapy, it is important to assess all pre-existing medical problems, such as diabetes, hypertension, and weight, and to screen all candidates for symptoms of depression and coronary artery disease. An acceptable plan for monitoring patients on antiviral therapy would include monthly visits during the first 12 weeks of treatment, followed by visits at three-month intervals until the end of therapy. At each visit, adherence to treatment, and the presence of any side effects should be reviewed. Laboratory monitoring should include measurements of the complete blood count and differential (if leucopenia has developed), ALT, AST, ALP, bilirubin (total and direct), INR, and Albumin every 4 weeks on treatment. Thyroid function (represented by Thyroid Stimulating Hormone (TSH)) should be measured every 12 weeks, and at six months after completing antiviral therapy. The monitoring of treatment effectiveness is based on repeated measurements of HCV RNA levels. With genotypes 1 and 4, HCV RNA level should be measured at baseline and in weeks 4, 12, and 24 (if HCV RNA positive at week 12) and week 48 of treatment. With genotypes 2 and 3, HCV RNA level should be measured at baseline, in weeks 4, 12 (if HCV RNA is positive at week 4), and 24. With all genotypes, HCV RNA should be ordered 24 weeks after documenting End of Treatment response (ETR) to verify the achievement of SVR. A sensitive real-time PCR-based assay with a lower limit of detection of 50 IU/ml should be used. The same assay should be used in each patient to determine HCV RNA at different time points, in order to ensure consistency of results.^[153]

Recommendations

1. In chronic HCV non-genotype 1 infected patients with normal renal function, combination therapy with pegylated IFN- α and ribavirin is considered the standard of care (Grade A).
2. After initiating combination antiviral therapy, patients should be seen at monthly intervals in the first three months, and then every two to three months until the end of treatment. Patients who have completed the treatment regimen should be seen six months after the end of treatment. Individualized close follow up should be planned, based on the severity of any adverse events (Grade D).

Adverse events associated with pegylated interferon and ribavirin

Pegylated interferon-related adverse events are the primary reason for patients discontinuing treatment. It is estimated that 10% to 14% of patients may discontinue treatment due to adverse events associated with the use of IFN.^[154,155] The most common of these are influenza-like side effects such as fatigue, headache, aching bones, myalgia, fever and rigors. Neuropsychiatric side effects may also manifest themselves in 22% to 31% of patients. These side effects include depression, anxiety, irritability and rarely psychosis. In addition, neutropenia (absolute neutrophil count (ANC) below 1500 mm³) is a frequent laboratory abnormality, occurring in 18% to 20% of patients, and severe neutropenia, that is, ANC < 500 mm³, may be observed in 4% of patients. Despite the decline of the neutrophil count, serious infections are not related to the degree of neutropenia.^[156,157] The use of peg-IFN can also induce autoimmune disorders, such as autoimmune thyroiditis,^[158] or could aggravate pre-existing autoimmune disorders.

The most common side effect related to RBV is hemolytic anemia. Anemia can be observed in approximately one-third of patients. Dose adjustment for anemia (hemoglobin level < 10 g/dL) may be required in 9% to 15%. Other side effects associated with RBV could include mild lymphopenia, hyperuricemia, itching, rash, cough and nasal stuffiness. RBV is teratogenic in animals, and therefore strict birth control should be practised in patients being treated with peg-IFN- α and RBV during treatment and for six months following its discontinuation.

Management of adverse events related to antiviral therapy

Table 3 summarizes common strategies used in ameliorating antiviral adverse events. Neutropenia and thrombocytopenia are common adverse events reported when peg-IFN- α is administered. The dose of pegylated interferon should be reduced if the ANC falls below 750/mm³, or if the platelet count falls below 50,000/mm³. When using peg-IFN- α 2a,

the dose may be reduced from 180 to 135 μ g/week, and then to 90 μ g/week. When using pegylated IFN- α 2b, the dose may be reduced from 1.5 to 1.0 μ g/kg/week and then to 0.5 μ g/kg/week. Peg-IFN- α 2b should be stopped if the platelet count is < 25,000. Once neutrophil or platelet counts rise again, treatment can be re-started, but a reduced dose should be administered. There is no evidence to support the routine use of granulocyte colony stimulating factor (G-CSF, Filgrastim) to reduce the rate of infections or improve SVR rates. Serious infections may occur in 3% to 5% of patients, irrespective of neutrophil count.^[156,157] The use of granulocyte colony-stimulating factors should therefore be reserved for managing only the most severe neutropenia which is not initially responsive to peg-IFN dose reduction.

Eltrombopag is an orally active thrombopoietin-receptor agonist that stimulates thrombopoiesis.^[159] It allowed successful treatment of HCV when given for 12 weeks to patients who had baseline thrombocytopenia (20,000 to 70,000 mm³). However, thrombopoiesis-stimulating drugs are not generally recommended for the management of thrombocytopenia, as there is still a lack of sufficient data on their role in improving SVR rates, as well as a potential risk of precipitating portal vein thrombosis.

Although anemia is most commonly related to RBV, Peg-IFN also contributes to anemia by its effect on bone marrow suppression. It manifests itself early, within the first 2 weeks of administration, with a mean maximum hemoglobin reduction of 3 g/dL in first 6-8 weeks that could be associated with an improved chance of achieving SVR.^[160] A decrease in hemoglobin of 1.5 g/dL at week 2 of therapy has been associated with the risk of severe anemia and the need for treatment interruption. If significant anemia occurs (hemoglobin < 10 g/dl) the dose of RBV should be adjusted downward, by 200 mg at a time. RBV administration should be stopped if the hemoglobin level falls below 8.5 g/dl. However, RBV dose reductions to levels less than 60% will significantly decrease the likelihood of obtaining SVR. Recombinant erythropoietins (rEPO) can therefore be used to maintain or improve hemoglobin levels, in order to avoid significant ribavirin dose reductions or interruptions. rEPO can be administered when the hemoglobin level falls below 10 g/dl. The hemoglobin level should be assessed 2 weeks after initiating rEPO. The rEPO dose should be reduced if the increase in hemoglobin is more than 1 g/dl, and stopped if the hemoglobin level rises to over 12 g/dl. The hemoglobin level should then be re-assessed 4 weeks later. The dose should again be reduced if the hemoglobin increase is more than 2 g/dl, compared to 4 weeks earlier. If the hemoglobin level falls again below 12 g/dl, erythropoietin therapy can be re-started at 50% of the initial dose. If the hemoglobin level rise is less than 1 g/dl at 4 weeks of administration and no other cause of anemia is found, the rEPO dose can be increased.

Table 3: Summary of management of other adverse effects of Peginterferon/Ribavirin

System	Adverse effects	Suggested management
Constitutional	Influenza like illness after injection including fatigue, fever, myalgia, headache. These tend to diminish and subside after 4–6 weeks of therapy.	NSAIDs or acetaminophen (<2 g/day) prophylaxis or treatment
Dermatologic	Common causes: hair loss, pruritus, dry skin, injection-site reactions, rash (maculopapular or erythematous), psoriasis, photosensitivity, dermatitis; rarely caused toxic epidermal necrolysis, Stevens-Johnson syndrome, angioedema, injection-site necrosis	Mild reactions can be managed with topical lotions, topical corticosteroids, or reassurance; discontinue therapy for serious skin reactions. Hair loss is reversible/temporary as hair grows back after completing antiviral therapy.
Ophthalmologic	Retinal abnormalities (subclinical), loss of visual acuity, visual field changes, blindness	Pre-treatment evaluation of patients at high risk (e.g., diabetes, hypertension, eye disease); discontinuation of therapy in case of retinopathy.
Thyroid	Hypothyroidism or hyperthyroidism	Monitor TSH every 3 months; thyroid replacement (levothyroxine) as needed for hypothyroidism; beta blockers for mild hyperthyroidism; discontinuation of therapy for severe hyperthyroidism and endocrinology consultation.
Cardiovascular	Myocardial ischemia due to stress, rarely cardiomyopathy	Pretreatment risk stratification; discontinue therapy after a cardiac event.
Pulmonary	Cough, shortness of breath, infectious pneumonia/bronchitis, rarely interstitial pneumonitis	Bronchodilators for cough if associated with wheeze; antibiotic therapy for bacterial pneumonia syndrome; discontinue therapy if interstitial pneumonitis occurs and refer to pulmonologist.
Gastrointestinal	Common causes: weight loss, anorexia, nausea, vomiting, abdominal pain, dyspepsia; rarely can cause pancreatitis, hemorrhagic colitis	Anorexia can respond to cannabinoids, although rarely used in practice; nausea can be managed by taking ribavirin with food, adding proton pump inhibitors, and if severe, 5-HT3 antagonists; pancreatitis or hemorrhagic colitis require discontinuation of therapy.

Source: CCO Hepatology in practice. Management of Hepatitis C Infection (Feld JJ, Shah H), available at www.inPractice.com. Reproduced with permission

However, few studies have prospectively evaluated the impact of rEPO on SVR rates. rEPO use was associated with an improved rate of SVR when higher doses of RBV (~15 mg/kg/day, 1,000–1,600 mg/day) were initiated, but showed no impact on SVR with standard ribavirin dosing.^[161,162]

The use of hematological growth factors is associated with increased cost of treatment for chronic hepatitis C.^[163] In addition, rEPO has been associated with serious side effects, including cardiovascular and/or thromboembolic events, pure red cell aplasia, progression of certain cancers, and death.^[164]

Antiviral treatment should be stopped immediately in cases of a hepatitis flare (ALT levels above 10 times normal), or if a serious bacterial infection occurs at any site in the body, regardless of neutrophil counts.

Interferons can induce or exacerbate depression. There are two distinct depressive syndromes that can develop while receiving interferon, namely, a depression-specific syndrome (mood, anxiety, cognitive complaints), and neurovegetative syndrome, (fatigue, anorexia, pain and psychomotor slowing). Depression-specific symptoms are responsive to serotonergic antidepressants, whereas neurovegetative symptoms are not.

Antidepressant therapy may be prescribed in a prophylactic approach to patients in whom pre-treatment screening indicates possible positive symptoms of depression. Success in reducing the incidence of depression without an impact on the SVR during treatment has been reported.^[165] IFN-induced sleep deprivation manifested together with irritability and anxiety should not be confused with depression, and should be managed with anxiolytics.^[166] Early consultation and follow up with a psychiatrist is desirable whenever psychiatric symptoms are suspected.

Recommendations

1. The peg-IFN- α and RBV should be temporarily interrupted if the ANC falls below 500/mm³, or hemoglobin falls below 8.5 g/dl respectively (Grade A). The combination of peg-IFN- α and RBV should be stopped if severe hepatitis flare or severe sepsis occur (Grade C).
2. The use growth factors is associated with an increased cost of therapy and a lack of sufficient evidence towards improvement of sustained virologic response (SVR) (Grade B). When deciding to use recombinant erythropoietin (EPO) and G-CSF, an 80% or more of RBV and peg-IFN- α dose should be maintained during the course of therapy so that the benefit of adherence

can be achieved (Grade D).

3. Peg-IFN- α - induced neutropenia does not correlate with increased frequency of infection episodes (Grade C). The use of granulocyte colony-stimulating factor (G-CSF) does not reduce the rate of infections (Grade C)

Improving treatment success rates

Before starting antiviral therapy, patients must be instructed about the schedule and the side effects to be expected during treatment. Patients should also be instructed about preventive and therapeutic measures to ease these side effects. Adherence to an antiviral treatment regimen is generally defined as taking $\geq 80\%$ of treatment regimen for $\geq 80\%$ duration of therapy. In order to maintain maximum exposure to each drug after dose reductions and hence, improve the response rate, a full dose should be resumed whenever possible.^[167] Diabetes control, weight reduction for obese^[168] and reduction of or abstention from alcohol intake are important measures to consider before initiating antiviral therapy.

Recommendations

1. In order to optimize SVR rates, complete adherence to both peg-IFN- α and RBV regimens should be emphasized (Grade B).
2. Pre-treatment weight reduction in obese individuals and good control of diabetes mellitus may increase the chance of SVR (Grade B).

TREATMENT OF CHRONIC HCV NAÏVE PATIENTS

Genotypes 1 and 4 HCV infection

The SVR reported by registration trials for peg-IFN- α was 46% and 42% in patients with HCV genotype 1 treated with peg-IFN- α 2a or peg-IFN- α 2b and RBV, respectively.^[154,155] The reported SVR rates using peg-IFN- α and weight based RBV in large prospective trials of genotype 4 were 54% to 68%.^[169-171] The optimal treatment regimen for HCV infection with genotypes 1 and 4 is peg-IFN- α based RBV (13-15 mg/Kg/day) divided into two doses, for a duration of 48 weeks. The dose of peginterferon alfa-2a (Pegasys[®]) is 180 μ g subcutaneously per week, and the dose of peginterferon alfa-2b (PegIntron[®]) is 1.5 μ g/kg subcutaneously per week. Direct acting antiviral agents (Boceprevir and Telaprevir) have recently been approved for use as triple therapy in chronic HCV genotype 1 infected patients^[172,173] (See section on triple therapy of HCV genotype 1).

Recommendations

1. Treatment with peginterferon plus ribavirin should be planned for 48 weeks; the dose for peg-IFN- α 2a (Pegasys[®]) is 180 μ g subcutaneously per week, and for peg-IFN- α 2b (PegIntron[®]) is 1.5 μ g/kg subcutaneously per week together with weight-based (13-15mg/kg/day) RBV (Grade A).

Genotypes 2 and 3 HCV infection

In patients infected with HCV genotypes 2 and 3, the reported SVR is 76% and 82% of cases treated with peg-IFN- α 2a plus RBV, and peg-IFN- α 2b plus RBV, respectively.^[154,155] A recent meta-analysis showed higher SVR rates in genotype 2 than in genotype 3 infected patients treated for 24 weeks (74% vs. 69%, respectively).^[174] Treatment with peg-IFN plus RBV should be administered for 24 weeks, using a fixed dose of RBV at 800 mg per day. However, those with a BMI beyond 25 or those who have baseline factors suggesting low responsiveness (high viral load, insulin resistance, metabolic syndrome, severe fibrosis or cirrhosis) should receive a weight-based dose of RBV, similar to genotypes 1 and 4.^[175]

Recommendations

1. Treatment with peg-IFN plus RBV should be planned for 24 weeks; the dose for peg-IFN- α 2a (Pegasys[®]) is 180 μ g subcutaneously per week, and for peg-IFN- α 2b (PegIntron[®]) is 1.5 μ g/kg subcutaneously per week, together with 800 mg RBV (Grade A).
2. Adequate RBV doses at 15 mg/kg should be administered to patients with genotypes 2 and 3 who have baseline factors that predict low responsiveness to peg-IFN, such as obesity and cirrhosis (Grade D).

Genotype 5 and 6 HCV infection

Patients with genotypes 5 and 6 infections are under-represented in trials of peg-IFN and RBV, due to their limited distribution globally. In the non-randomized retrospective studies of genotype 5 that are limited to small numbers of patients, the reported SVR, using 24-48 weeks non-pegylated and pegylated IFN and RBV, was 48% to 60%.^[176-178] The reported SVR rate in HCV-6 patients treated with a 48-week regimen of peg-IFN and RBV varies between 66% and 86%.^[179-181] There are insufficient data to determine the optimal treatment regimen for genotypes 5/6, and further studies are needed. Until robust data are available, the treatment regimen for patients with genotype 5 / 6 infections should follow the recommendations for patients with genotype 1 and 4 infections, using peg-IFN and a weight-based dosage of RBV, over a period of 48 weeks.

Recommendations

1. Treatment with peg-IFN plus ribavirin should be planned for 48 weeks; the dose for peg-IFN- α 2a (Pegasys[®]) is 180 μ g subcutaneously per week, and for peg-IFN- α 2b (PegIntron[®]) is 1.5 μ g/kg subcutaneously per week, together with a weight-based dosage of RBV (Grade C).

Direct-acting antivirals in treatment naïve patients

In many patient populations, the outcome of standard HCV therapy with peg-IFN- α and RBV is not satisfactory. The advanced knowledge of the structures of HCV polymerases

and proteases has meant that structure-based drug design can be used to develop direct inhibitors to these enzymes. This category of antivirals is called “direct-acting antivirals” (DAAs).

Currently, many drugs at different stages of development are under investigation. Of these, Telaprevir and Boceprevir are NS3/4A protease inhibitors. Each has been the subject of several large recently completed multicenter phase 3 clinical trials, and they have subsequently been added to some international institutional guidelines for the treatment of HCV genotype 1.

The efficacy of telaprevir in combination with peg-IFN- α 2a and RBV in the treatment of naïve HCV genotype 1 patients has been evaluated in several phase 2 and 3 studies. A landmark phase 3 (ADVANCE) trial,^[173] evaluated the efficacy of telaprevir with peg-IFN- α 2a and RBV in 1088 treatment-naïve patients with genotype 1 chronic HCV. Patients were randomly assigned to one of three different treatment regimens. SVR rates were significantly higher (69% to 75%, versus 44%) in patients who received a regimen containing telaprevir, in comparison with a standard of care treatment regimen. The most commonly encountered adverse events in the telaprevir-based groups were pruritus, rash, and anemia.

Another (ILLUMINATE) trial,^[182] was a phase 3 non-inferiority trial, designed to evaluate differences in SVR rates between a 24-week period and a 48-week period of telaprevir-based therapy in patients who had an extended rapid virologic response (eRVR; HCV RNA < 25 IU/mL at both weeks 4 and 12). In this trial, a total of 540 treatment-naïve patients with HCV genotype 1 were included. The overall SVR rate was 72%, and an eRVR was achieved in 65%. Among patients with an eRVR, the SVR rate in the 24-week treatment group (92%) was non-inferior to the SVR rate in the 48-week treatment group (88%).

Boceprevir is another NS3/4A protease inhibitor. Its efficacy against HCV genotype 1 was evaluated in several trials. A phase 3 SPRINT-2 trial studied boceprevir in combination with peg-IFN- α 2b and RBV in 1097 treatment naïve genotype 1 HCV patients.^[172] All patients received a 4-week lead-in of peg-IFN- α 2b and RBV. They were subsequently randomly assigned to 3 groups: group 1 (the control group) received placebo plus peg-IFN/RBV for an additional 44 weeks, group 2 received boceprevir plus peg-IFN/RBV for 24 weeks, and those with a detectable HCV RNA level between weeks 8 and 24 received placebo plus peg-IFN/RBV for an additional 20 weeks, group 3 received boceprevir plus peg-IFN/RBV for 44 weeks. SVR was achieved in 125 of the 311 patients (40%) in group 1, in 211 of the 316 patients (67%) in group 2 ($P < 0.001$), and in 213 of the 311 patients (68%) in group 3 ($P < 0.001$).

These drugs appear promising in the treatment of HCV genotype 1. However, they are limited by their proven efficacy against HCV genotype 1 only; in addition, concerns about their side effects and long term resistance profile exist. Preclinical data suggests that, with the currently used dosages, boceprevir might not be effective in HCV genotype 4. In a proof-of-concept study, telaprevir has shown activity against HCV genotype 4 during 15 days monotherapy or in combination with peg-IFN and RBV when compared to peg-IFN, RBV and placebo.^[183]

Recommendations

1. The combination of peg-IFN/RBV is the approved standard of care for chronic hepatitis C, especially non-genotype 1 (Grade A)
2. The most effective regimen for treating HCV genotype 1 is the use of triple therapy, with boceprevir or telaprevir in combination with peg-IFN/RBV (Grade A)

Clinical trials of HCV antiviral therapy in Saudi Arabia

When peg-IFN was internationally introduced, early, multiple trials were performed in Saudi Arabia. Shobokshi *et al.*, treated 180 HCV genotype 4 patients in a randomized open label multicenter trial. The first group received 180 μ g peg-IFN α 2a weekly, plus 800 mg/day RBV for 48 weeks, the second group received peg-IFN monotherapy, and the third group was treated with standard IFN- α 2a 4.5 MU TIW plus 800 mg/day of RBV. At the end of the follow up, SVR was seen in 50% of the patients in the peg-IFN combination therapy group, compared with 28% in the peg-IFN monotherapy group, and 30% in the standard IFN combination group.^[184] Al Faleh *et al.*, randomized 96 patients with fixed doses of either 100 μ g of peg-IFN- α 2b plus 800 mg/day of ribavirin or standard IFN plus RBV combination therapy. SVR was achieved in 43.8% of patients in the peg-IFN arm and in 29.2% of patients in the standard IFN arm. These results did not achieve statistical significance, probably because of the relatively small sample size.^[185] A retrospective study by Al Ashgar *et al.*, was performed on peg-IFN- α 2a and RBV in 335 patients with chronic hepatitis C, of whom 54.5% were genotype 4, and 22.15% genotype 1. The SVR was 55.1%.^[186] Another retrospective study by Dahlan *et al.*, on 240 patients who received peg-IFN- α 2a or peg-IFN- α 2b with standard dose of RBV, undertaken between 2003-2007, found that 64% of patients with genotype 4 had SVR.^[187]

Response-guided therapy of chronic HCV infection

The rapidity with which a patient clears HCV RNA during therapy has very important implications for predicting the likelihood of a response to treatment, for determining the optimal duration of treatment, and as a stopping rule for antiviral therapy. In patients infected with HCV genotype 1

and 4-6, HCV RNA levels should be assessed at the following times: baseline, week 4, week 12, and at the end of treatment. Week 24 HCV RNA testing is indicated in patients who do not obtain negative HCV RNA at week 12, i.e., in partial early virological responders (pEVR). In patients infected with HCV genotypes 2 and 3, HCV RNA levels should be obtained at baseline, week 4 and week 24. Week 12 HCV RNA level should be tested in patients who do not achieve rapid virological response (RVR). All HCV patients who achieve end of treatment response (ETR) should have their HCV RNA level tested six months after completing antiviral therapy, in order to establish whether SVR has been achieved, or relapse has taken place.

Rapid virological response

A rapid virologic response (RVR) is defined as having undetectable HCV RNA in serum after the first 4 weeks of antiviral therapy. The achievement of an RVR identifies those patients who are most sensitive to IFN, and is highly predictive of obtaining an SVR, independent of genotype and treatment regimen; an SVR rate of 91% is reported.^[188] Approximately 20% of persons with HCV genotypes 1 and 4 infections and 66% with HCV genotype 2 and 3 infections achieve an RVR.^[189,190]

Early virologic response and delayed virological response

Early virologic response (EVR) is defined as a greater than 2-log drop in viral load at 12 weeks of therapy. An EVR is sub-classified into a complete EVR (cEVR), defined as undetectable HCV RNA in serum at 12 weeks of therapy, and a partial EVR (pEVR), defined as a greater than 2-log decrease in the level of HCV RNA in serum at week 12 of therapy.

Approximately 97% to 100% of treatment-naive patients with HCV genotype 1 infection who do not achieve EVR, fail to obtain an SVR.^[191,192] In contrast, an EVR is less accurate in predicting an SVR. A complete EVR is a better predictor of an SVR than a 2-log reduction in HCV RNA. The clinical utility of an EVR is less useful in persons with HCV genotype 2 and 3 infections, since the majority clear virus by week 12 and respond to treatment. In patients with detectable HCV RNA (≥ 50 IU/ml) at week 24, i.e., partial virological response, treatment should then also be stopped, due to a small chance of SVR (1–3%).^[192,193] Delayed virological response (DVR), also known as slow virological response, is defined as a more than 2 Log₁₀ drop in HCV RNA level at week 12 (pEVR) but with an undetectable level at week 24, and maintained undetectability to the end of treatment.

Stopping rules for combination therapy with peginterferon and ribavirin

All HCV patients who have null response [defined as > 2

log reduction in HCV RNA level at week 12 but detectable viral load (> 50 IU/ml) at week 24] must abandon antiviral therapy.

INDIVIDUALIZED TREATMENT DURATION ACCORDING TO ON-TREATMENT VIROLOGIC RESPONSE

Shortening the duration of antiviral therapy based on RVR

It may be possible to shorten the duration of treatment for patients with genotypes 1 or 4 who achieve an RVR, from 48 to 24 weeks.^[194,195] Treatment for those patients with genotypes 2 or 3 who achieve an RVR, could possibly be shortened to 16 weeks from 24.^[196-199] However, a large, multicenter international trial^[199] randomly assigned 1469 patients with HCV genotypes 2 or 3 to receive 180 μ g of peg-IFN- α 2a weekly, plus 800 mg of RBV daily for a period of either 16, or 24 weeks. The SVR rate was significantly lower in patients treated for 16 weeks than in those treated for 24 weeks (62% vs. 70% respectively). In addition, among those patients treated for 16 weeks only, there was a higher relapse rate (31% versus 18%). Shortening the duration of antiviral therapy across all genotypes should not be attempted if patients have any of the following negative predictors: high viral load (genotypes 1 and 4 > 600,000 IU/mL, genotypes 2 and 3 > 400,000 IU/mL), advanced fibrosis of $\geq F3$ on metavir, insulin resistance, metabolic syndrome, and non-viral steatosis or HIV co-infection.

Extension of duration of antiviral therapy based on DVR

Strategies to improve SVR rates in patients who achieve undetectable HCV RNA between weeks 12 and 24 of therapy, delayed virologic response (DVR), or so-called slow responders, may include extension of duration of therapy for another 24 weeks. For patients with genotypes 1 and 4 infection who have DVR, consideration could be given to extending treatment to a duration of 72 weeks, with the intention of minimizing the risk of relapse.^[200-204] However, in the era of direct acting antiviral therapy, all genotype 1 infected patients are expected to undergo triple therapy, and therefore extension of the treatment for another 24 weeks would probably not be necessary, due to the normally impressive SVR rate obtained with triple therapy. In patients with genotypes 2/3 infection with no RVR, treatment of 48 weeks duration is advised.^[175] Insufficient data exist for other genotypes.

Recommendations

1. A highly sensitive quantitative HCV RNA PCR with a lower limit of detection of 50 IU/ml or less should be

- used when treating HCV infection (Grade A).
- Before initiating antiviral therapy, patients must have genotyping performed. Knowledge of the HCV genotype will determine the dose of ribavirin and treatment duration (Grade A).
 - Antiviral therapy must be discontinued if patients fail to achieve more than 2 log reduction in HCV RNA at week 12 of treatment (Null response) (Grade A). Patients who achieve more than 2 Log reduction in HCV RNA at week 12 but remain detectable (≥ 50 IU/ml) at week 24 should discontinue treatment (partial response) (Grade A).
 - Shortening the duration of antiviral therapy in patients who achieve RVR should also be attempted in patients who lack pretreatment negative predictors (Grade B).
 - Extension of antiviral therapy to 72 weeks should be considered in HCV genotype 1 and 4 patients if delayed virological response is obtained (Grade A). Similarly, patients with genotypes 2 and 3 who have no RVR with pre-treatment negative predictors may be considered for extension of the treatment to 48 weeks (Grade C).

RE-TREATMENT OF EXPERIENCED CHRONIC HCV PATIENTS

Poor adherence to antiviral regimen by patients, and inappropriate dose reductions can both contribute to low response rates. Significantly, 20% to 50% of patients treated with peg-IFN and RBV will not achieve an SVR.

Null responder and partial responder

Approximately one third of patients treated with peg-IFN and RBV are unable to obtain negative viremia before week 24. These patients may be either null responders, or partial responders. The decision to engage on a repeated course of therapy must be individualized for each patient in the light of potential benefits, when options are limited, and the chances for success quite low. Non-responders to previous non-peg-IFN can be retreated with peg-IFN- α -2a or 2b and RBV. Re-treatment with peg-IFN and RBV has been shown to result in an SVR rate of 40% among patients who were previously treated with IFN monotherapy, but this rate dropped to 10% in those who had previously received combination therapy with non-peg-IFN and RBV.^[205-207] Re-treatment of patients who failed to respond fully to a previous full treatment regimen of peg-IFN- α / RBV with the same or a different peg-IFN regimen, showed disappointing results, and is not recommended.^[208] Given the unfortunate SVR rate for re-treatment of HCV patients, all non-responders genotype 1 and relapsers to previous peg-IFN treatment should be considered for triple therapy using protease inhibitors.^[209,210] Re-treating non-responders for a longer duration improved response rates, although in general the rates remained disappointingly low. In the REPEAT trial,^[211] extension of peg-IFN- α 2a therapy to 72 weeks in patients who had previously been treated with peg-

IFN- α 2b (the study included all genotypes, but genotype 1 was the predominant one) showed an SVR rate of 16%, compared with 8% of those who received 48 weeks of treatment. The major limitation of the REPEAT study was that 64% of patients had an unknown response to their previous peg-IFN therapy. Non-genotype 1 patients with DVR in the first cycle of treatment who have evidence of inadequate exposure to either peg-IFN- α or RBV (due to dose adjustments or poor adherence during the first course of therapy) could be considered for re-treatment with peg-IFN- α and RBV. Non-responders to peg-IFN and RBV with baseline cirrhosis should generally undergo screening and surveillance for HCC and varices.

Relapsers

The reported relapse rate after treatment with peg-IFN- α and RBV is approximately 15–25%. Patients who relapsed after treatment with standard IFN-based regimens responded to re-treatment with peg-IFN- α and RBV in 32–53% of cases.^[206] Re-treatment with peg-IFN- α 2a of patients who relapsed after prior peg-IFN and RBV was reported in a small, open-label, multicentre trial, which included 28 relapsers, of whom 68% then achieved SVR.^[211] All genotype 1 patients who have relapsed after a previous peg-IFN course should be considered for re-treatment with triple therapy using protease inhibitors.^[208,209]

Recommendations

- HCV patients with non-genotype 1 infection experiencing prior non-response or relapse after non-peg-IFN therapy with or without RBV, or previously treated with peg-IFN monotherapy, may be considered for a second course of therapy with peg-IFN plus RBV (Grade B).
- HCV patients with non-genotype 1 infection who had previously shown a null or partial response pattern, where an adequate dose of peg-IFN and RBV had been administered during the first course of antiviral therapy, should not be subjected to another course of combination therapy using same or different peg-IFNs (Grade B). These patients should be followed up for progression of liver disease and could wait for new, more effective protease inhibitors (Grade C)
- Non-responder or relapsers patients with genotype 1 HCV infection after treatment with either peg-IFN or non-peg-IFN should be considered for re-treatment with a triple therapy regimen, using direct acting antiviral agents (Grade A).

Role of maintenance antiviral therapy in non-responders

Studies assessing the role of peg-IFN as a maintenance strategy for non-responders^[212,213] failed to demonstrate any significant reduction in the clinical endpoints such as progression of fibrosis, HCC, or death.

Recommendations

1. Maintenance therapy with peg-IFN is not recommended for patients with bridging fibrosis or cirrhosis who have previously failed a course of peg-IFN and RBV (Grade A).

DIRECT-ACTING ANTIVIRALS IN TREATMENT-EXPERIENCED HCV PATIENTS

With the arrival of new, direct-acting antiviral (DAA) drugs like telaprevir and boceprevir, which have been shown to be more effective than re-treatment with a standard regimen, re-treatment of prior non-responders is now promising.

Recently, two phase 3 studies have evaluated telaprevir. The first was in a prior non-responders, PROVE 3 (Protease Inhibition for Viral Evaluation) study, and the second, the REALIZE study (Re-treatment of Patients with Telaprevir-based Regimen to Optimize Outcomes).^[210] In both trials, results after re-treatment of prior non-responders with different telaprevir regimens in combination with peg-IFN- α 2a and RBV were superior to those for re-treatment with peg-IFN- α 2a and RBV alone.

The SVR rates ranged from 51% to 66% in the regimens containing triple therapy (telaprevir, peg-IFN and RBV), and better response rates were demonstrated in relapsers when compared to non-responders. In these trials, the SVR rates ranged from 69% to 88% in prior relapsers, while lower SVR rates in non-responders of 29% to 39% were observed. The majority of patients in these trials had genotype 1 infection.

Boceprevir addition also showed similar improvements in response rates for treatment-experienced individuals. The addition of boceprevir to peg-IFN and RBV resulted in significantly higher rates of SVR in previously treated patients with chronic HCV genotype 1 infection, when compared with those on a regimen of peg-IFN and RBV alone.^[209]

In a phase 3 trial (RESPOND-2), boceprevir was evaluated in prior partial responders or relapsers with peg-IFN and RBV; however, null responders were not included in this trial. A 4-week lead-in phase of peg-IFN and RBV and response-guided therapy was required with different regimens of boceprevir and with peg-IFN- α 2b and RBV. SVR rates were higher in the two boceprevir groups (group 2, 59%; group 3, 66%) than in the control group (21%, $P < 0.001$).

A retrospective analysis of null responders (defined as < 1.0 log₁₀ IU/mL reduction in HCV RNA after 4 weeks of peg-IFN- α 2b/RBV) to peg-IFN and RBV from the two lead-in groups of the SPRINT-1 trial was conducted. Following the lead-in phase, patients received 24 or 44 weeks of boceprevir plus peg-IFN- α 2b/RBV. An SVR was achieved in 25% and

55% of null responder patients treated with 24 or 44 weeks of triple therapy.

Although this analysis pertains to null responders assessed after only 4 weeks of peg-IFN and RBV, the majority of these patients would have failed to achieve an SVR. These findings suggest that the additional use of protease inhibitors are not the answer for this difficult-to-treat population.

There are ongoing trials with other DAAs that could suggest further solutions for the treatment of non-genotype 1 HCV patients with prior non-response.^[214,215]

Recommendations

1. Patients with HCV genotype-1 who have failed prior standard therapy with peg-IFN- α and RBV, can be treated with triple therapy with boceprevir or telaprevir, together with peg-IFN- α and weight-based RBV (Grade A).

TREATMENT OF ACUTE HEPATITIS C

Identification of clinical acute HCV infection is uncommon, since, most of the time it has a subclinical course with mild or no symptoms. When clinically suspected, a patient with possible acute HCV should be tested as soon as possible for HCV RNA, since the antibody testing requires several weeks for sero-conversion.

In the absence of a recent negative HCV test, discriminating between acute HCV and recently discovered chronic HCV is difficult. Spontaneous clearance of acute HCV infection can occur in up to 30% of cases, so the decision to treat or to delay treatment should weigh the possible chance of spontaneous resolution and the cost and possible side effects of treatment. In most instances, clearance will occur in the first 12 weeks, and the presence of symptoms predictive of spontaneous clearance can occur in about 30% of patients.^[216,217]

Treatment of acute HCV has been shown to reduce the development of chronic HCV infection; however, there is no consensus on the optimal treatment regimen. Therapy begun before 12 weeks have passed since diagnosis is associated with a better chance of SVR.^[218] Standard IFN alfa is effective in improving biochemical outcomes, and achieving sustained virologic clearance in 32% of IFN-treated patients, versus only 4% of control group patients.^[219] Several clinical trials have shown that the treatment of hepatitis C infection during the acute phase is associated with high SVR rates ranging between 75% and 95%.^[220] Twelve trials were analyzed (414 patients) in a meta-analysis. The use of standard interferon appeared to significantly increase the SVR (risk difference 49%; 95% confidence interval 32.9-65%) in comparison to patients on no treatment.^[221]

Several studies have evaluated the use of peg-IFN. Once weekly peg-IFN- α 2b monotherapy (1.5 μ g/kg per week) for a period of 12 weeks was evaluated in a major study of 129 subjects with acute HCV. The SVR rates were 95%, 92%, and 76% with treatment onset at 8, 12, and 20 weeks, respectively. The overall SVR rate was 87%.^[218] Patients infected with genotypes 2, 3, and 4 showed better SVR rates than those infected with genotype 1. The role of combination therapy with RBV is not well established, and probably does not improve SVR; however, it might be considered in cases where chronic infection is suspected.^[222,223]

The impact of the duration of therapy with 12 weeks vs. 24 weeks on SVR rate has also been evaluated in several case series, but no definitive recommendation can be made about the optimal length of treatment needed for acute hepatitis C. It is however, advisable to treat for 24 weeks.^[224]

Recommendations

1. There is no clear evidence on the optimum timing for the start of acute HCV therapy, but treatment can be delayed up to 12 weeks after acute onset of hepatitis to allow for spontaneous resolution (Grade B).
2. Treatment with either standard IFN or peg-IFN- α monotherapy for 24 weeks is recommended; however, peg-IFN- α is preferable because of its convenience in administration (Grade B)

TREATING SPECIAL POPULATIONS

Treatment of patients with severe liver disease

Patients with hepatitis C-compensated cirrhosis need to be treated to prevent complications, especially in the absence of contraindications. Indeed both large cohort studies and meta-analyses have shown that an SVR in patients with advanced fibrosis is associated with a significantly decreased incidence of clinical decompensation and HCC. However, the SVR rates with interferon-based therapy are lower in patients with advanced fibrosis than in those with mild to moderate fibrosis.^[154,155,225] In the study done by Heathcote *et al.* on patients with compensated cirrhosis, it appeared that the SVR was reached in 30% of those treated with peg-IFN- α 2a alone,^[226] and in another study by Helbeling *et al.* after they added two different doses of RBV (1,000 to 1,200 mg per day or 600 to 800 mg. per day), an SVR was achieved in 52% and 38% of patients respectively.^[227] Dose reduction was necessary in 78% and 57% of subjects, and serious adverse events developed in 14% and 18% respectively of the two groups.

Patients with advanced fibrosis usually have low leukocyte and platelet counts secondary to portal hypertension and hypersplenism and need close monitoring for side effects of medication. Medication-related hematological side effects may contraindicate therapy, and it is more evident (vs.

frequent) and anticipated in cirrhotic than in non-cirrhotic patients.^[228] The use of growth factors might be useful in treating patients with advanced fibrosis, which offers the possibility of treatment with full doses of interferon-based therapy, the eradication of pre-transplantation HCV, and the lower likelihood of post-transplantation infection.^[229-231] Some studies on patients with decompensated cirrhosis preliminary to liver transplantation have been done. In the earliest reported study, done by Crippin *et al.* in 2002, over half of considered patients were found ineligible because of cytopenias.^[232] In 2007, Iacobellis *et al.* carried out a controlled study,^[233] in which peg-IFN- α 2b, was given in doses of 1.0 μ g/kg body weight per week, and RBV in doses of 800 to 1000 mg daily for 24 weeks; 44% and 7% of patients with genotypes 2 or 3 and genotypes 1 or 4, respectively developed SVR. Treatment was tolerated in 41% reduced in 39% and discontinued in 20%. Over a 30-month follow-up period, only 23% of patients with an SVR decompensated, while 83% of the control group and 62% of the non-responder group developed decompensation. The conclusion of this study was that in decompensated cirrhotics, HCV clearance by therapy is lifesaving and reduces disease progression.^[229,234,235] Approximately 75% of patients rendered HCV RNA negative at the time of transplantation, remain negative post-transplantation. Surveillance for HCC and portal hypertension should be done regularly, irrespective of SVR achievement, which in turn translates to a decreased rather than an abolished risk when HCV infection has been eradicated.

Recommendations

1. Compensated cirrhotics should be treated to prevent future complications (Grade A).
2. Treatment should be started carefully, with close monitoring for side-effects, and lower dosages might be used once the patient has been placed on a liver transplant list, aiming for HCV clearance prior to transplantation. However, this approach is applicable in only around 50% of patients, and tolerance is poor, particularly in patients with decompensated cirrhosis (Grade C).
3. Cirrhotics should undergo regular surveillance for HCC, irrespective of SVR (Grade B).

Post-Liver transplantati on recurrence

Treatment of established graft lesions with peg-IFN and RBV combination therapy results in a SVR in around 30% of patients.^[236] Most studies initiated therapy at least 6 months post-operatively, in order to optimise patient tolerance and to enable the addition of RBV.^[237]

Since the first deceased donor liver transplantation (DDLT) took place in 1990, more than 300 DDLTs have been performed in Saudi Arabia. More recently, more than 200 living donor liver transplantations (LDLTs) have been performed in Saudi Arabia. However, there is inadequate

documentation of the natural history of HCV re-infection after liver transplantation in the Kingdom and worldwide.^[238]

HCV infection recurrence is universal in patients, and tends to be more aggressive when there is detectable HCV RNA at the time of liver transplantation.^[229] The course of HCV-related liver disease is accelerated in liver transplant recipients, and almost 6% to 23% of patients develop cirrhosis after a median of 3.4 years.^[239-241]

Successful therapy has been shown to have a positive impact on both graft and patient survival.^[242] Rates of SVR have been lower than those achieved in the non-transplant setting. Possible reasons for this difference include high HCV viral load post-LT, a higher frequency of genotype 1 patients, poor tolerance of treatment after LT, and the need for frequent dose reductions. Treating a patient pre-emptively before the biochemical and histological recurrence of hepatitis seems attractive theoretically, because of low viral levels but the results were not encouraging. The safety efficacy and patient tolerance of peg-IFN- α alone, or associated with RBV, given pre-emptively, have been evaluated in two randomized trials, with SVR rates of 8%^[243] and 18%,^[244] respectively. Although peg-IFN- α 2a^[245] or 2b^[244] plus RBV were deemed safe and were reasonably well tolerated, both demonstrated very poor efficacy early post-LT.

Only 40% to 60% of patients are candidates because of the high doses of immunosuppressive drugs used, underlying cytopenias, mild renal dysfunction and the presence of other medical problems during this early period post-liver transplantation, all of which can have an impact on efficacy. Monotherapy with standard or pegylated IFN is not advised because of poor SVR rates, as reported in several randomized controlled trials.^[243,246,247] Small, uncontrolled, trials of peg-IFN plus RBV report SVR rates of 18% to 19%.

The presence of significant fibrosis or portal hypertension one year after transplantation is predictive of rapid disease progression and graft loss.^[244] Most transplant centers prefer to delay therapy until recurrent disease is confirmed, either by persistently raised ALT levels unexplained by other causes, or by the demonstration of significant fibrosis on liver biopsy (Metavir and IASL stage ≥ 2 or Batts-Ludwig and Ishak stage ≥ 3).^[248] The decision to treat should therefore take into consideration the benefit of good SVR rates versus the risks inherent in achieving these (precipitate acute cellular rejection and side effect of therapy). The threshold for performing a liver biopsy should be low, in order to assist treatment decisions, and whenever liver tests worsen during the course of antiviral therapy, to diagnose this, and to use it to further influence treatment decisions. Data on post-transplant HCV genotype 4 treatment is scarce. A single center in Saudi Arabia reported twenty-five patients infected

with HCV genotype 4 infections that were treated with peg-IFN- α 2a at a dose of 180 $\mu\text{g}/\text{week}$ in addition to 800 mg/day of RBV (the dose was adjusted within the tolerated range of 400-1,200 mg). Pre-treatment liver biopsies were obtained from all patients. Biochemical and virological markers were assessed before, during, and after treatment. Twenty-two patients (88%) achieved EVR (12 patients tested negative for HCV-RNA). Fifteen (60%) and fourteen patients (56%) achieved an ETR, and a SVR, respectively. Five patients had advanced pre-treatment liver fibrosis. Pre-treatment ALT was elevated in 24 patients (96%). The most common adverse effects were flu-like symptoms and cytopenia. Eighteen patients (72%) required erythropoietin alpha and/or granulocyte-colony stimulating factors as a supportive measure. One patient developed severe rejection complicated by sepsis, renal failure, and death. Other adverse effects included depression, mild rejection, impotence, itching, and vitiligo.^[249] No studies using protease inhibitors in the post-transplant setting have yet been published but are ongoing; however, other drug interactions with immunosuppressants is of major concern and needs to be taken into consideration.^[250]

Recommendations

1. Once chronic hepatitis C recurrence has been documented histologically after liver transplantation, cautious treatment by an experienced physician should be started (Grade A).
2. Urgent initiation of treatment in patients with significant fibrosis one year after transplantation that predicts rapid disease progression and graft loss (Grade B).
3. Liver biopsy while on treatment is indicated, if liver enzymes worsen, to rule out graft rejection, although it is rare (Grade C).

HIV co-infection

Approximately 25% of HIV-infected persons in the western world have chronic HCV infection.^[38] No clear data from Saudi Arabia on treating such group seems to exist. Progression of liver disease is accelerated in patients with HIV-HCV co-infection, in particular in those with a low CD4-positive cell count and impaired immune function. For this reason, early antiretroviral therapy should be considered in patients with HIV HCV co-infection.^[251] Patients with HIV should be tested for the presence of HCV by doing anti-HCV and HCV RNA tests, especially in those patients with HIV and unexplained abnormalities in liver function tests and enzymes. The treatment regimen is the same as that for patients without HIV co-infection. The dose of RBV should always be weight-based, and the duration of treatment up to 48 weeks, which could be extended in some genotype 1 patients to 72 weeks. Co-administration of RBV with didanosine (ddI) should be avoided to prevent mitochondrial toxicity and fatal lactic acidosis. Anemia is more pronounced during therapy with

IFN plus RBV when the patient is also taking zidovudine (AZT). This suggests that there is a cumulative myelosuppressive effect of IFN plus AZT that further reduces erythropoiesis that could compensate for the acute RBV-induced hemolysis.^[252] HIV patients with decompensated cirrhosis should be assessed for liver transplantation if no contraindication exists.

Recommendations

1. Treatment regimen is the same in HIV co-infected and non-HIV infected patients but the dose of ribavirin should always be weight-based (Grade B).
2. Treating HCV in co-HIV infected patients may require longer treatment duration (72 weeks for genotype 1 and 48 weeks for genotypes 2 and 3) (Grade B).
3. Before using RBV, the physician should make sure that patients are not on AZT, or ddI (Grade C).

HBV co-infection

In HBV endemic areas, co-infection with HBV and HCV can be seen in people who have a high risk of parenteral infections, such as injection drug users,^[253] patients on hemodialysis,^[254] patients undergoing organ transplantation^[255] and HIV-positive individuals.^[256] In patients with HCV-HBV co-infection, HCV is usually the main driver of chronic hepatitis activity. Although it may fluctuate, the HBV DNA level is often low or undetectable. Due to the variety of virological profiles in HBV/HCV co-infection, it is important to assess the dominant virus prior to initiating therapy, and after hepatitis delta virus infection has been excluded. The HCV dominant virus should be treated with peg-IFN- α and RBV following the same rules as mono-infected patients. The SVR rates in this group are broadly comparable or even higher than those in HCV mono-infected patients.^[257,258] There is a potential risk of HBV reactivation during or after HCV clearance.^[259] In that case, or if HBV replication is detectable at a significant level, concurrent HBV nucleoside/nucleotide analogue therapy may be indicated.

Recommendations

1. Treatment regimen is the same as for mono-infected patients (Grade B).
2. Concurrent HBV nucleoside/nucleotide analogue therapy is indicated if there is a significant HBV replication at any stage, pre-, peri- and post-HCV clearance (Grade C).

Treatment of patients with renal disease

Chronic renal disease represents a global health problem. Chronic HCV infection is prevalent in patients with end-stage renal disease (ESRD) on hemodialysis (HD), and in renal transplant recipients, with significant impact on morbidity and mortality. The prevalence rates reported in HD patients in Middle Eastern countries are 68% in Saudi Arabia with a range of 14.5% to 94.7%, 26% in Oman, and 80% in

Egypt.^[251] Patients with HCV infection and chronic renal disease are prone to develop diabetes mellitus^[260] and *denovo* glomerulonephritis post-transplantation. Additionally, HCV-infected subjects have a shorter graft survival after renal transplantation, due to increased risk of severe infection and liver disease deterioration.^[261] Accordingly, there is a general belief that these patients should be treated before transplantation.^[262] Treatment with current standard combination therapy is challenging in patients with ESRD, due to its tolerability. Liver biopsy may be needed before treating those patients, because of the discrepancy between the level of the ALT and the extent of histologic damage that is noted in such patients.^[263] At present, therapy for hepatitis C in patients with ESRD is controversial, and should be considered only in patients waiting for renal transplantation, those with significant liver disease, and minimal comorbid conditions that may affect survival, and in patients with acute hepatitis C. The therapeutic regimen varies with the severity of the kidney disease. Persons with creatinine clearance of more than 60 ml/minute can be treated like those patients without kidney disease. RBV is cleared by the kidneys; therefore hemodialysis patients have been treated with peg-IFN- α monotherapy.^[264] Since peg-IFN- α 2a is cleared through the liver and peg-IFN- α 2b primarily through the kidneys,^[265] there could be a theoretical accumulation of peg-IFN- α 2b when used in hemodialysis, although hemodialysis does not appear to affect clearance.^[245,266] Even though this has not been formally compared, no obvious differences are observed clinically. Most experts support the cautious use of peg-IFN- α , adjusting the dose to the level of renal dysfunction.

Although the current practice is to administer the full dose of peg-IFN- α , the recommended starting doses for this group are peg-IFN- α 2b, at 1 μ g/kg subcutaneously once weekly or peg-IFN- α 2a, 135 μ g subcutaneously once weekly. In the absence of RBV, SVR rates are substantially lower, and careful patient selection and side effect management are important. Most studies used a 6-month post therapy SVR as the end point for successful therapy. Overall, 40% of HCV treated patients had an SVR, including 31% for genotype 1, a rate greater than that reported for IFN monotherapy.^[187] In a single-center study of Saudi hemodialysis patients, peg-IFN- α 2a was found to be well tolerated, and hematological disturbances appeared to be the most important adverse effects.^[267] At the end of therapy, a response rate of up to 76%, with 69% sustained response was obtained with Peg-IFN- α 2a therapy. In an earlier study by Huraib *et al.*, HCV RNA became negative in 76% of patients after 12 weeks of treatment, in 88% after 12 months of treatment, and in 71% of the patients, 6 months after completion of therapy. Of 13 patients who underwent liver biopsies after 6 months of therapy, 11 patients (85%) showed histological improvement.^[268]

However, the use of peg-IFN and RBV in dialysis patients is hampered by fairly common side effects. Combination treatment with peg-IFN- α and RBV might be considered by experienced physicians and used with caution in those with creatinine clearance below 50 ml/minutes,^[269] with individualized RBV dosing of 200-800 mg/day, and titrating the dose based on creatinine clearance and hemoglobin level decline during the first few weeks of therapy. These patients may need substantial hematopoietic support, as suggested by few preliminary studies.

HCV post renal transplantation

HCV has been recognized as one of the major causes of morbidity and mortality, and indicates a poor prognosis for patient and graft survival in renal transplantation. It is also associated with an increased risk of cirrhosis and its complications. Treatment of chronic HCV infection with peg-IFN- α and RBV in renal transplant recipients is associated with a risk of acute or chronic cellular rejection, resulting in graft loss and reduced patient survival.^[270] Accordingly, routine interferon-based antiviral treatment post-renal transplant should be considered only for selected patients, and those who develop post-transplantation fibrosing cholestatic hepatitis.^[271] Subjects being considered for renal transplantation should be treated for hepatitis C prior to transplantation.

The largest retrospective study on 19 patients with stable graft function and absence of cirrhosis was reported by Aljumah *et al.*, between October 2003 and December 2008, where the patients received peg-IFN- α 2a/2b and RBV for 48 weeks, with a SVR rate of 42.1%. Only one patient had graft rejection (5.3%).^[272] The result was encouraging, and another prospective protocol involving 28 adult renal transplant recipients at two centers in Saudi Arabia, ≥ 12 months after transplant surgery with confirmed HCV and evidence of histological disease (METAVIR $\geq A2/F2$; $\geq F3=17$) were recruited in a pilot open-label trial and given peg-IFN- α 2a (135–180 $\mu\text{g}/\text{week}$, based on GFR) plus RBV (200–1200 mg/day, based on GFR). Safety and laboratory assessments were performed weekly for 4 weeks, then 2-weekly for 8 weeks, and then 6-weekly for 36 weeks. Renal biopsy was performed in patients with a 20% increase in serum creatinine from pre-treatment levels. Twenty seven patients completed at least 12 weeks of therapy, and 21 completed all study assessments. Dose reductions of peg-IFN and RBV were required in 36% and 54%, respectively for hematological side effects. Overall, 55.6%, 38.5% and 19% achieved EVR, end-of-treatment response and SVR, respectively. None of the patients experienced any rejection episodes during or 24 weeks after therapy and the authors concluded that peg-IFN/RBV therapy in renal recipients is safe, but has limited efficacy in the treatment of chronic HCV, and as such larger prospectively conducted multicenter studies in this population subset are needed.^[273]

Treatment of patients with cryoglobulinemia-associated glomerulonephritis

Cryoglobulinaemia refers to the presence of abnormal immunoglobulins in the serum, which have the unusual property of precipitating at temperatures below 37°C and re-dissolving at higher temperatures. Cryoglobulins (CGs) are classified, on the basis of their clonality, into three types. Type II CGs and type III CGs (mixed cryoglobulinaemia) are highly prevalent in patients with chronic HCV infection. Mixed cryoglobulinaemia (MC) can be found in 29-54% of patients with HCV infection according to different studies.

MC can be associated with systemic vasculitis, renal impairment and peripheral neuropathy. Treatment of HCV related cryoglobulinemia is challenging, and should be restricted to symptomatic patients in order to avoid unnecessary complications like exacerbation of vasculitis in patients with cryoglobulinemia-associated glomerulonephritis during treatment by interferon.^[274,275] Improvement of clinical MC is reported in 50% to 70% of patients receiving antiviral therapy based on IFN- α and RBV, and correlates with the reduction of HCV RNA concentrations.^[276,277]

Antiviral therapy should thus be considered as the first line therapeutic approach in HCV-infected patients with MC-related disorders. However, with multi-organ involvement, antiviral therapy may have to be limited due to the severity of a specific MC-related disorder, treatment failure, side effects or contraindications. In such cases, other therapeutic strategies, such as immuno-suppression and/or plasmapheresis should be considered.

Persons with progressive renal failure generally require treatment with immunosuppressive therapy, steroids and plasmapheresis.^[278] The role of IFN-based antiviral therapy can be considered for those with mild to moderate kidney disease, or after controlling the acute flare with immunosuppressive agents.^[279] Most of the studies regarding the treatment of MC are small and uncontrolled, thus there is no evidence-based data on which to base firm recommendations. It is therefore suggested that persons with moderate proteinuria and slowly progressive kidney disease can be managed by means of a regimen of one year of low dosage RBV (200 mg-800 mg/d) in combination with IFN- α or peg-IFN- α , and in most cases this is well tolerated by HCV patients, and leads to SVR and significant improvement of GFR.^[280]

Recommendations

1. Liver biopsy should be individualized if the decision is made to treat HCV in a chronic renal disease patient (Grade C).
2. The same standard combination antiviral therapy can be

used to treat persons with chronic HCV infection and mild renal disease (GFR >60 mL/minute) (Grade C).

3. Non-hemodialysis patients with severe renal disease can be treated cautiously with reduced doses of both peg-IFN (alpha-2a, 135 µg/week; alpha-2b, 1 µg/kg/week) and RBV (200-800 mg/day) (Grade C).
4. Patients on hemodialysis can safely be treated with peg-IFN-monotherapy (Grade A).
5. Combination treatment with individualized doses of RBV can be considered in selected patients (Grade C).
6. Patients on a renal transplant list should be treated prior to transplantation to avoid the risk of treatment-induced acute graft rejection post-transplantation (Grade B).
7. Treatment is recommended post-renal transplant only in selected patients and those with fibrosing cholestatic hepatitis (Grade C).
8. Patients with cryoglobulinemia and mild to moderate proteinuria or slowly progressive renal disease can be treated with either standard IFN or reduced doses of peg-IFN-α and RBV (Grade C).
9. Patients with cryoglobulinemia and marked proteinuria with evidence of progressive renal disease or an acute flare of cryoglobulinemia can be treated with rituximab, cyclophosphamide plus methylprednisolone, or plasma exchange, followed by interferon-based treatment once the acute process has subsided (Grade C).

Alcohol and drug abuse

Chronic alcohol consumption in patients with chronic hepatitis C is associated with an accelerated fibrosis progression, cirrhosis, and an increased risk of HCC.^[281] SVR rates are lower in patients with alcohol abuse.^[281] Patients regularly consuming alcohol should not be excluded from treatment, but should receive counseling to stop their consumption, and additional support to improve regimen-adherence during therapy. Illicit injection drug use is the predominant mode of HCV transmission and little data are available on the treatment of active drug users. Patients should be drug-free for at least 6 months before treatment, and close monitoring by an experienced multidisciplinary team of hepatologists and addictologists to be sure that they will adhere to treatment and regular follow-up visits is necessary.^[282]

Recommendations

1. Alcohol consumption should be strongly discouraged (Grade A).
2. Patients on stable maintenance substitution can be treated for HCV in an interdisciplinary team who need to also consider their slightly reduced SVR-rates when compared to conventional HCV patients, as the treatment should be individualized (Grade B).
3. Illicit drug users should continue receiving support and counseling parallel to HCV treatment (Grade C).

Treatment of persons with psychiatric illnesses

The increasing use of IFN for treating patients with hepatitis C has resulted in recognition of and increasing concern about the psychiatric side effects that can result from treatment. These effects can occur either shortly after beginning IFN therapy, or later, as a result of continued treatment. Patients may report some psychiatric illness during the course of their treatment, such as depression, anxiety, and occasional suicidal ideation, and a high percentage of previous drinkers and drug users tend to relapse. A combination of some or all of these factors would lead to an argument against treating this population. Significant depressive symptoms occur in 21% to 58% of IFN-treated patients. Case studies have demonstrated that pharmacologic interventions are beneficial in reducing iatrogenic psychiatric symptoms, while allowing patients to maintain IFN therapy.^[283]

Former or current drug abuse and mental disorders are considered risk factors. In addition, reports of suicide attempts during IFN-α therapy and the risk of reinfection has led to the opinion that the use of IFN-α is contraindicated for patients with a preexisting mental disorder, ongoing opiate abuse, or methadone substitution. As a consequence, most of these patients remain untreated, despite fulfilling the medical criteria for antiviral treatment of chronic hepatitis C.

However, a recent prospective controlled trial^[284] provided evidence that treatment of chronic hepatitis C infection with peg-IFN-α and RBV is possible in different subgroups of “difficult-to-treat” psychiatric patients, and treating them in interdisciplinary treatment units in order to optimize adherence and response rates and to manage side effects is recommended. Most psychotropic agents are thought to be safe. However, consideration should be given to drug interactions and dose modification in patients with advanced liver disease.

Recommendations

1. Patients with HCV infection and concomitant mental and psychiatric disorders can be considered for treatment using the currently approved regimens (Grade C).
2. Treatment of hepatitis C infection in patients with psychiatric disorders should be undertaken only with the support of a multi-disciplinary team that should include psychiatric counseling services prior to therapy (Grade C).

Hemoglobinopathies

Thalassemia major, which requires frequent blood transfusions, and sickle cell disease are among the common hemoglobinopathies that challenge the physician. These patients have higher incidence of anemia and iron accumulation when treated with standard combination Hepatitis C therapy.

They can however, be treated with standard combination therapy, but these complications should be carefully managed with growth factors, blood transfusions, and iron chelation therapy when needed.^[255] Chronic HCV infection is frequent in individuals with sickle cell anemia (SCA). They have life-long anemia, chronic hemolysis, and at times also have hematological crises, which can worsen the anemia and require chronic transfusions. The HCV antibody positivity is directly related to the number of transfusions given, and on average the prevalence rate in transfused patients is more than 10%. It is known that the combination of iron overload and HCV can lead to a more rapidly progressive liver disease. The treatment of HCV in sickle cell patients poses a challenge to clinicians. A novel approach described by some is the pre-treatment of these patients with hydroxyurea to increase fetal hemoglobin, therefore decreasing the severity of RBV-related hemolysis. Individual cases have been successfully treated with a combination of peg-IFN- α and RBV. In one study in Saudi Arabia, fifty-two patients with SCA and HCV were treated over a period of 7 years. All were treated with peg-IFN and a standard dose of RBV for 24 weeks for those with genotype 2 and 3 infections, and for 48 weeks for those with genotype 1 and 4 infections. Only 8 were receiving hydroxyurea at the time of treatment. All tolerated the treatment well and none experienced a decrease in their Hb, which required blood transfusion before, during or after therapy. There were no hematological side effects attributable to RBV at the usual recommended dose. Thirty-seven (71.2%) achieved SVR. The authors showed that patients with SCA and HCV can be treated with peg-IFN and RBV at the usual recommended dose, including those who are not receiving hydroxyurea. The conclusion from this study was that treating HCV infection in SCA patients is considered to be safe and effective, and the response rates in these patients are comparable to those of patients without SCA.^[256]

In addition, a case series from the western province of Saudi Arabia enrolled 8 patients with chronic HCV infection and SCA, who were treated with peg-IFN- α -2a and RBV for one year. All 8 patients had a cEVR. Seven out of the 8 patients had an ETR of whom, 5 achieved SVR. Hemoglobin concentrations measured at 1, 3, 6, 9, and 12 month intervals during their treatment showed no significant changes from those measured at baseline. The study was able to conclude that treatment of chronic HCV hepatitis in patients with SCA with peg-IFN- α -2a and RBV seems safe and effective.^[257]

Recommendations

1. Patients with hemoglobinopathies can be treated with combination therapy, but need careful monitoring for hematologic side effects (Grade C).

CONCLUSIONS

The SASLT guideline for HCV provides a concise, updated, evidence-based review of the diagnosis and management of chronic HCV infection in Saudi Arabia. This may help to initiate plans to prevent HCV infection in the population, to bring about early and accurate diagnosis of patients, and to facilitate appropriate and timely referrals between primary, secondary, and tertiary care providers. This guideline also aims to help identify gaps in the knowledge and understanding of the incidence of HCV in Saudi Arabia requiring further research. As noted above there is a large population of patients with few therapeutic options, and DAA therapy has become the focus of investigations and once additional information is available, this guideline needs to be updated.

Disclosures

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