# CONSENSUS GUIDELINES FOR THE MANAGEMENT OF

# HEPATITIS C INFECTION

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The conference jury wrote the conclusion and recommendations contained in this document, in full independence

# *CONSENSUS GUIDELINES COMMITTEE FOR THE MANAGEMENT OF HEPATITIS C INFECTION*

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# SUMMARY

At prevalence of 2.7% in the early 1990's, it is estimated that approximately 500,000 people in Saudi Arabia have been exposed to the hepatitis C virus (HCV). Over 80% of such individuals remain infected and most of them progress to chronic hepatitis C (CHC), cirrhosis, and/or hepatocellular carcinoma (HCC). The incidence of newly acquired hepatitis C infection in Saudi Arabia has declined with the recent reported prevalence of approximately 1%. This decline is largely due to the early implementation of testing of blood donors for HCV. However, it is pertinent that measures are taken to identify patients already infected and offer treatment to those with good prognostic factors. Hepatitis C genotype 4, the most predominant genotype in Saudi Arabia (62%) has been resistant to conventional interferon (IFN) therapy and sustained response rate to combination therapy with IFN plus ribavirin (RBV) has been poor.

The recently completed Ministry of Health (MOH) clinical trial reports improved sustained virological response (SVR) rate of 65.2% among week 12 early responders of HCV genotype 4 chronic hepatitis patients using pegylated (PEG)-IFN alfa-2a (40 KD) plus RBV. This encouraging process calls for a change in patient management towards a more community-based approach. With the aim of assessing these changes and defining a management strategy for HCV infected patients in Saudi Arabia, a consensus conference was held and consensus guidelines issued. The final recommendation will be made available to all MOH, tertiary and non-government hospitals in the Kingdom to provide uniform care to all CHC patients.

Based on the SVR of the above mentioned clinical trial, the committee recommends treatment for patients with histologically proven CHC, with elevated serum alanine aminotransferase (ALT) and positive HCV ribonucleic acid (RNA). Patients with normal serum ALT may not be treated if liver histology is normal or reveals only minimal changes. Patients with decompensated cirrhosis should not be treated.

Hepatitis C virus genotype 4 patients should be treated with combination therapy of PEG IFN alfa-2a (180 µg/week) plus RBV (1000-1200 mg daily according to body weight) for 48 weeks. Patients with HCV non-genotype 4 may also be treated with combination therapy of PEG-IFN plus RBV, but genotypes 2 and 3 patients can be treated for 6 months only. Stringent monitoring for virological and biochemical responses is eminent and provides the opportunity to interrupt treatment at week 12 in non-responders.

A strong counseling program should be available for untreated patients, relapsers and non-responders. An exit program for liver transplantation should also be set up. It is likely that some of the consensus recommendations will have to be revised in the short-term, as the results of ongoing studies become available.

Future research in advances in diagnosis, pathogenesis, natural history, management and prevention should be encouraged and newer therapies for CHC patients should be sought for non-responders.

## GOALS

His Excellency Professor Ossama Shobokshi, called for a Consensus Workshop on Management of HCV with the following goals:

* To review the scientific advances and the current controversies surrounding HCV infections.

* To produce a consensus statement and prepare appropriate guidelines for the management of CHC infection in Saudi Arabia, especially for genotype 4, the most dominant genotype in KSA. Taking into consideration the growing recognition of the seriousness of the disease, the diversity of the virus, the high cost of treatment, the improvement in response to therapy and the potential for adverse events associated with drug therapy.

The following questions were particularly addressed:

* Which patients should be treated?

* What are the appropriate laboratory tests to be used for diagnosis and monitoring of patients?

* What is the optimal therapy?

* How should patients be monitored?

* How should relapse and non-response be managed?

## PREAMBLE

Hepatitis C virus-RNA positive patients are at risk of developing chronic liver disease (CLD), cirrhosis and HCC. Approximately, 10-20% of such patients develop liver cirrhosis, and 1-2% develop HCC. Seroprevalence data in the Kingdom of Saudi Arabia (KSA) indicates that there may be as many as 500,000 people that have been exposed to HCV, of whom 400,000 are at risk of long-term liver disease. Therefore, HCV infection represents a significant health problem for the country. National data indicates that HCV accounts for 35-50% of causes of CLD among Saudi patients.

Given the risk of disease and the burden of infection in KSA, these persons will need counseling to understand the importance of the diagnosis. They represent a source of infection to others and should be advised as to the steps necessary to prevent transmission to their spouses and other members of their family. Fortunately, HCV is not easily transmitted outside certain areas of medical practice (such as hemodialysis and transfusion units).

Patients infected with HCV will be identified through antibody testing (anti-HCV) usually as part of the investigation of illness but also as part of screening. Not all antibody sero-positive persons will be viremic, and further testing for the virus genome (HCV-RNA) is needed to confirm current infection. Tests for HCV-RNA should ideally be carried out more than once if there is any suspicion of acute infection, as a significant proportion of patients with acute HCV infection will clear the virus spontaneously. Continued detection of HCV-RNA will confirm the chronic infection. A physician who has experience in the management and treatment of HCV infection should evaluate these patients. This is usually a gastroenterologist/hepatologist.

The mechanism by which HCV causes hepatic pathology is not known. There is no accessible in-vivo animal or in-vitro cell culture system for this virus. Hepatitis C virus is thought not to be cytopathic in its own right and the hepatocyte damage is considered to be immune mediated through a cytotoxic T cell response (CTL) against a number of virus specific antigens expressed by the liver cells. Due to continuing hepatocyte damage and death, fibrosis develops over time and this, if given enough time, may progress to cirrhosis. This fibrosis is accelerated in the presence of other hepatitis virus infections, in the face of immuno-suppression (iatrogenic, human immuno-deficiency [HIV] co-infection) and by the ingestion of hepatotoxic substances such as pharmaceutical agents and ethanol.

During the assessment of the patient, the overall liver damage is usually, but not invariably, determined by histological examination. Those who should have liver biopsy are described below. The degree of necro-inflammation and the extent of fibrosis are the 2 most important measures of the activity of the disease.

Treatment of HCV infection, as recommended below, using a combination of the cytokine IFN and the RNA polymerase inhibitor RBV, will lead to clearance of the infection (SVR).

Early trials showed that IFN alone had some favorable effect but were disappointing as many patients failed to show virus suppression and even in those in whom the virus was suppressed, HCV-RNA reappeared during treatment or after the end of treatment (EOT). Overall, IFN monotherapy is, with some exceptions detailed below, no longer considered as adequate therapy. The response to therapy is influenced to variable degrees by lower baseline viral levels, less inflammation and fibrosis and lower body mass.

Viral genotype has a significant effect on the outcome of treatment, whether this is IFN monotherapy or IFN/RBV combination therapy. Determination of genotype is therefore, important to define both the likelihood of a sustained response to therapy and anticipated duration of therapy. Even where one genotype of the virus predominates, as in KSA, minor populations of other genotypes are present and it is considered appropriate to determine the genotype before starting treatment. It is useful to have some measure of the likelihood of successful treatment. This is important in the counseling of the patient and may lead to therapeutic policies that generate some degree of cost containment.

The past decade has witnessed major advances in our knowledge of the epidemiology, diagnosis and treatment of HCV infection. There is better understanding of the natural history of the infection including the risk factors that may affect disease progression. The availability of PEG-IFN, especially when used in combination with RBV has dramatically improved the response rate to therapy. Public health campaigns in relation to hepatitis have led to increased awareness among the population.

The results of several surveys within KSA in the past, have indicated that the seroprevalence of HCV was approximately 3% in apparently healthy blood donors and 0.2% in children. However recently, HCV seroprevalence is on the decline, ranging from 0.1% in children, 0.7% in women and 1.1% in adult males. In patients with HCV-related chronic hepatitis, genotype 4 is the most common accounting for 62% compared to genotype 1 (24%), genotype 2 (7%) or genotype 3 (6%), see **Table 1**.

Table 1 - Hepatitis C genotypes/subtypes in the chronic hepatitis C patients in the Kingdom of Saudi Arabia.

| Nationality | N | 1 | 1a | 1a/b | 1b | 2 | 2a/c | 2b | 3 | 3a | 3c | 4 | 4a | 4b | 4c/d | 4e | 4f | 4h | 5a | 10a |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Saudi N (%)** | **353** | 9 (2.5) | 18 (5.1) | 1 (0.3) | 57 (16.1) | 4 (1.1) | 20 (5.7) | 2 (0.6) | 1 (0.3) | 19 (5.4) | 1 (0.3) | 108 (30.6) | 2 (0.6) | 8 (2.3) | 68 (19.3) | 13 (3.7) | | 20 (5.7) | 1 (0.3) | 1 (0.3) |
| **Non-Saudi N (%)** | **139** | | | | 4 (2.9) | | 4 (2.9) | 2 (1.4) | | 5 (3.6) | 1 (0.7) | 57 (41) | 2 (1.4) | 2 (1.4) | 40 (28.8) | 5 (3.6) | 1 (0.7) | 15 (10.8) | 1 (0.7) | |

Earlier trials in Saudi Arabia have shown a poor response of CHC genotype 4 to IFN monotherapy (<10%) and to IFN combined with RBV (<30%). Thus, HCV genotype 4 was considered relatively resistant to IFN therapy. However, a recent efficacy and safety clinical trial in Saudi Arabia, in which 180 CHC patients of genotype 4 were treated with 3 different regimens for 48 weeks, was carried out as follows:

* Group A: PEG-IFN alfa-2a (40 KD) 180 µg qw plus RBV (400 mg) bid.
* Group B: PEG-IFN alfa-2a (40 KD) 180 µg qw.
* Group C: IFN alfa-2a (Roferon® A) (4.5 MIU) tiw plus RBV (400 mg) bid.

Among week 12 early responders, SVRs at 72 weeks were 65.2% and 47.2% in the 2 PEG-IFN groups and sustained biochemical responders were 69.6% and 69.4% in groups A and B.

Despite the use of low dose RBV, SVR among intend to treat (ITT) early responders were very encouraging for our genotype 4 CHC patients.

## TREATMENT OF PATIENTS WITH CHRONIC HEPATITIS C

### Identification and selection of patients for treatment

The Kingdom of Saudi Arabia has an efficient health care system by which services are provided to the population at no cost. The manner in which the HCV-infected patient is identified in the KSA is varied. It is recommended that efforts are made to extend the recruitment of HCV-infected persons into MOH sponsored programs of clinical management as widely as possible. Many, but not all, will come through medical consultation for investigation of possible liver disease. Others will be identified through a number of KSA screening programs, including those for blood donors, pre-marriage and pre-employment testing and testing during hospitalization and before entry to penal institutions. However, if this is to be successful, attempts must be made to ensure that the social, sexual, and employment aspirations of those found to be infected are not unnecessarily jeopardized. This will require care, and compassion from all involved. It is worth targeting certain sections of the population who may be at risk of HCV infection (hemophiliacs, thalassemics, blood-product recipients, organ-transplant recipients, hemodialysis patients and drug addicts).

It is possible that a national HCV awareness campaign using the media could also assist in bringing others forward.

A referral system from primary health care through the general hospitals to tertiary centers ensures the access of patients to the best treatment available. As part of the preventive strategy against viral hepatitis, blood donor screening for anti-HCV had been practiced for the last decade. This has provided the opportunity to identify asymptomatic HCV seropositive individuals among voluntary blood donors. These should be referred to specialized units for further evaluation, counseling and possible treatment (see below). In this regard, 2 major groups of patients are identified; those with clinical, or biochemical evidence of CLD (for example, elevated ALT) and those with no clinical abnormalities and with normal ALT.

Only patients confirmed to have HCV-RNA in serum will be eligible for therapy.

All patients diagnosed as having HCV-positive CLD should be evaluated for treatment in units with experience in the management of HCV and liver diseases.

Treatment of the HCV-infected patient with anti-viral drugs aims at best to terminate the infection and cure the patient from HCV infection. Reduction in liver inflammation may benefit the patient, even if the infection is not eradicated. The aims of therapy therefore are to:

* Terminate viral infection, and clear HCV-RNA from the liver and the plasma.
* Prevent or delay the progression of liver disease.
* Reduce the risk of HCC.
* Improve the quality of life.

### Selection procedures

Patients with chronic HCV infections can, for the purpose of treatment, be divided into categories according to the clinical stage of disease:

*Category 1: HCV-RNA positive with elevated ALT.*

Adults (18-65 years) with chronic hepatitis who are positive for HCV-RNA and who have persistently elevated serum ALT (> 1.5 times upper normal level on 3 occasions within a 6-month period) should be treated. The identification of HCV genotype is warranted, but its non-availability should not delay therapy. Liver biopsy is strongly recommended before the initiation of therapy to assess the degree of liver inflammation and fibrosis.

*Category 2: HCV-RNA positive with normal ALT.*

Up to 30% of patients with CHC will have persistently normal serum ALT levels. When biopsied, up to 25% of patients with persistently normal ALT levels will have significant inflammation or fibrosis. Generally, the level

of serum ALT correlates poorly with histological inflammatory activity or fibrosis. If a decision to treat is being considered, genotyping and liver biopsy will be useful in determining the duration of treatment and the stage of liver disease. In patients with persistently normal ALT levels, the risk of disease progression is low and there is little information on the long-term benefits from treatment. Until further information becomes available, no therapy is recommended if the histology is normal or shows mild changes (F1 fibrosis). Patients with significant abnormal histology (F2 or F3 fibrosis) may be considered for treatment. The natural history of patients with genotype 4 with persistently normal ALT, treated or untreated, needs to be determined from carefully planned longitudinal studies. This data will be important for future therapeutic and preventive strategies in KSA.

*Category 3: Advanced liver diseases and liver cirrhosis.*

Patients with decompensated liver cirrhosis (defined as the presence of jaundice, ascites, bleeding varices, or hepatic encephalopathy) should not be treated with IFN and RBV. Patients who are compensated should be carefully evaluated for possible treatment, taking into consideration the stage of their disease and the presence of co-morbid conditions and viral co-infections. Such treatment should be offered within approved clinical trials, with identifiable end points, particularly if it relates to HCV genotype 4 infections.

*Category 4: Relapsers (recurrence of detectable HCV-RNA in serum within 6 months post treatment) and non-responders (persistence of detectable HCV-RNA during or at the end of treatment).*

Relapsers: Patients who were treated with standard IFN or received incomplete courses of treatment and who achieved EOT response but failed to sustain it, should be treated with PEG-IFN and RBV. Severity of the disease and tolerability of drug therapy should be taken into consideration when making the decision to treat. Those who relapsed after treatment with PEG-IFN and RBV may have little benefit from a repeated therapy with the same regimen. Therefore, such patients should be considered only for inclusion in clinical trials of newer drugs.

Non-responders: Those who failed to achieve an EOT response to monotherapy (IFN) or combination therapy (IFN plus RBV) or incomplete courses of treatment of any type should be retreated with PEG-IFN/RBV. Non-responders to a full course of combination therapy based on PEG-IFN and RBV are unlikely to further benefit by extending the duration of therapy and should not be treated except as part of clinical trials.

**Special categories**

*Children*

Children with HCV infection (mostly perinatally acquired) without HIV and hepatitis B virus (HBV) co-infection have a relatively good prognosis. In childhood, the virus rarely causes symptoms. Unless there are clinical signs of severe liver disease, investigations other than routine liver function tests and HCV-RNA detection are not indicated before the age of 5 years. Hepatitis C virus-infected children above 5 years of age should have a liver biopsy to assess the extent of liver inflammation and fibrosis. If the histological activity index indicates moderately severe or severe liver disease, treatment should be given. The safety of RBV in children needs to be addressed.

Treatment of choice is the same as for adults but with some differences. Both IFN and RBV are used, in doses adjusted according to the child's weight. The course for HCV genotype 2 and 3 infections is of 6 months duration; for other genotypes, the recommendation is to treat for 12 months.

Sustained virological response rate based on combination therapy of IFN plus RBV, ranging from 38% for genotype 1 and 82% for genotypes 2 and 3 have been reported. Sustained virological response data regarding combination therapy of PEG-IFN plus RBV in children is awaited.

There is no data on HCV genotype profile and the response of various genotypes to therapy in children in KSA. Similarly, there is no data on which to base stopping treatment in those who do not show a viral response at 12 weeks of therapy. For these reasons, it is recommended that children should only be treated in tertiary treatment centers. Genotypes should be determined at the time of initial assessment. Clinical response to treatment and related data should be collated and analyzed centrally. This will provide useful information.

*Hemodialysis patients*

Data on IFN treatment of chronic HCV infection in hemodialysis patients is limited. Patients who are enrolled in a transplant program and waiting transplantation have been treated with the objective of viral clearance. A study conducted locally among dialysis patients reported a good response to standard IFN monotherapy. Clearly, larger studies are needed. Pegylated IFN and RBV are relatively contraindicated in patients with established renal failure. However, therapy of chronic HCV in this sub group of patients should be considered carefully. Such is the need for pretransplant viral clearance that therapies using PEG-IFN plus low dose RBV are being attempted in special units where clinical protocols can be carefully supervised.

*Co-infections with HBV and HIV*

Concomitant HCV and HBV infection, or HCV and HIV infection may accelerate the progression of liver disease. Combination therapy should be offered to these patients if they meet the aforementioned criteria, though the treating physician should be aware of the problem related to pharmacological interactions.

*Acute infection*

It is estimated that approximately 80% of acute hepatitis C will become chronic, if untreated. Some studies have indicated that early IFN treatment of acute infection prevents persistence of infection. However, small sample sizes and non-randomization limited these studies. Acute hepatitis C is usually sub-clinical and therefore, patients rarely present for diagnosis and treatment. It is recommended that serological and virological investigations are undertaken to confirm clinically suspected acute hepatitis C. The diagnosis is made most easily by:

* Seroconversion (enzyme immunoassay [EIA] negative to EIA positive)
* An evolving RIBA pattern of reactivity (this requires careful interpretation by an experienced serologist)
* Or changes in HCV-RNA.

There is no data on the outcome of IFN therapy in relation to acute HCV genotype 4 infection. Patients in this category may be offered treatment, as part of clinical trials, in a specialized unit.

*Organ transplant patients*

Pre-liver transplant patients are usually those with decompensated liver disease. Treatment of these patients can be potentially life threatening. Therefore, consideration of IFN therapy in this group of patients should be left to liver transplant units.

Pre-renal transplant patients (see above under hemodialysis):
IFN therapy in the post-renal transplant patients carries the risk of graft rejection and therefore is relatively contra-indicated.

## PRETREATMENT ASSESSMENT

Doctors experienced in the management of virus-related liver diseases must carefully evaluate patients being considered for treatment. The clinical assessment should include search for any of the extrahepatic manifestations that may be related to HCV or of immunologic origin.

**Clinical evaluation must include the following**

* Demographic data (for example age, gender, height, weight, nationality, occupation)
* Risk factors (blood transfusion, organ transplant, intravenous drug use)
* Date and mode of infection (if known)
* Symptoms and signs of CLD
* Co-morbidity (diabetes, schistosomiasis, thyroid disease, neuropsychiatric disorders and autoimmune diseases)
* Drug history (for example contraceptives, antihypertensives and oral antidiabetic drugs)

**Laboratory investigations should include:**

* Liver function tests: Transaminase [ALT/AST], gamma-glutamyl transpeptidase, alkaline phosphatase, total bilirubin.
* HCV EIA/RIBA
* HCV RNA (qualitative)
* Hematological indices: Complete blood count
* Coagulation profile: Prothrombin time and partial thromboplastin time
* Renal function tests: Urea, creatinine and electrolytes
* Anti-nuclear antibodies, anti-smooth muscle antibodies, anti liver-kidney microsomal antibodies and anti-mitochondrial antibodies, α-1antitrypsin, ceruloplasmin
* Thyroid function tests: Thyroid stimulating hormone, triiodothyronine, Free thyroxine
* A baseline alpha fetoprotein level
* Abdominal ultrasonography
* Urinalysis
* Exclusion of HAV, HBV, HEV, HIV, EBV
* Pregnancy test
* Serum bank (storage)

**Virology**

The preferred sample for virological investigation is plasma from a tube anti-coagulated with ethylenediamine tetraacetic acid (EDTA). The plasma is suitable for both antibody and HCV-RNA testing. If plasma is unavailable, then serum should be separated at low speed centrifugation and stored at -20$^0$C or lower.

*Detection of HCV antibodies by the enzyme immunoassays*

The enzyme immunoassay (EIA) is the methodology of choice to detect antibodies against HCV specific antigens in individuals exposed to HCV. The EIA assays should have adequate sensitivity, appropriate specificity and robustness. A negative EIA test is sufficient to exclude a diagnosis of chronic HCV infection in immuno-competent patients. The initial EIA-reactive (IR) result has to be confirmed. Firstly, the test should be repeated so that the serological reaction is shown repeatably reactive (RR). This sample is then considered to be "EIA-positive." The patient should be re-bled and re-tested using the same reagents to confirm that the first EIA-positive sample did indeed come from the patient. Then, the RR EIA-positive sample should be referred to a reference laboratory for confirmation of infection by PCR. If HCV-RNA is detected, CHC is confirmed. In those cases where HCV-RNA is not detected, the patient could have either, resolved past HCV infection, or a false-positive HCV EIA test result.

The EIA assays are considered to have very high specificity of over 99%. In our experience, studies of EIA-positive samples in KSA have shown that they are very likely to be reactive by RIBA, and the positive predictive value of our EIA assays reaches 97%. The EIA may be falsely negative in immuno-compromised patients (for example HIV, renal failure and post transplant) and in the early stages of an acute infection. Therefore, the HCV-RNA detection should be carried out in suspected cases.

*HCV-RNA detection*

Viral RNA detection tests for HCV can be either qualitative or quantitative. It is recommended that the blood sample should be taken into tubes with the anticoagulant (EDTA), which provides more stable RNA.

The HCV-RNA qualitative test is usually the more sensitive and can detect less than 50 IU/mL (<100 copies/mL) using target amplification assays such as reverse transcriptase-polymerase chain reaction (RT-PCR). Transcription mediated amplification (TMA), a newly developed technique has been shown to be more sensitive with a limit detection of less than 5 IU/mL. Because of this relative sensitivity, a qualitative assay will confirm viremia and assess the EOT and the SVR. Quantitative tests should be used to determine the pre-treatment viral load and to assess the early response to therapy at 12 weeks.

*HCV genotyping*

Pre-treatment HCV genotyping is important in the assessment of the predictability of the response to therapy and in the determination of the duration of treatment. For example, patients infected with genotypes 2 and 3 respond more favorably to therapy, with 70-80% SVR rates, whereas those with genotype 1 and 4 have a lower sustained response rate.

*Liver biopsy*

Liver biopsy is necessary to evaluate the stage and the grade of the disease. Although liver biopsy is not mandatory, it is strongly recommended in all cases, particularly, for patients who:

* are viremic but have normal ALT and who are being considered for treatment.
* have failed to respond at 12 weeks and who have not been previously biopsied.
* have persistently elevated liver enzymes despite clearance of viremia with therapy.

## CONTRAINDICATIONS

Treating doctors should familiarize themselves with the following clinical conditions that may be absolute or relative contraindications to the use of IFN or RBV and counsel patients accordingly:

* Hypersensitivity to the active substance or any of the ingredients
* Hypersensitivity to alfa-IFNs
* Autoimmune chronic hepatitis
* Severe psychiatric disorders
* Pre-existing thyroid abnormalities that are difficult to stabilize
* Decompensated liver disease
* Organ transplantation (other than liver)
* Uncontrolled seizures, central nervous system dysfunction, or both
* Pregnancy

## DRUG SELECTION FOR THE TREATMENT OF PATIENTS

**Combination therapy**

Based on the results of MOH clinical trials involving HCV genotype 4 patients in KSA and other countries, the combination of PEG-IFN and RBV is now considered the standard therapy for genotype 4, the most predominant genotype in KSA. This should be used in the treatment of chronic HCV, except where the use of RBV is contraindicated. The regular IFN in combination with RBV is sub optimal treatment and may be used only if PEG-IFN is unavailable.

*Hepatitis C virus genotype 4 treatment*

Pegylated IFN alfa-2a (40 KD) at 180 µg weekly for 48 weeks has been evaluated and proven to be safe and efficacious in KSA and is recommended for the treatment of HCV genotype 4 chronic hepatitis patients. The assessment of efficacy and safety of PEG-IFN alfa-2b in HCV genotype 4 chronic hepatitis cases is ongoing, and results will be evaluated in the near future. Conventional IFN can be used at the dose of 3-6 MU subcutaneously 3 times weekly.

*Hepatitis C virus genotypes other than 4*

The recommended doses are 180 µg weekly (48 weeks for genotype 1 and 24 weeks for genotypes 2 and 3) for PEG-IFN alfa-2a (40 KD) and 1.5 µg/kg body weight weekly (48 weeks for genotype 1 and 24 weeks for genotypes 2 and 3) for PEG-IFN alfa-2b (12 KD). The efficacy of both PEG-IFNs (IFN alfa-2a [40 KD] and IFN alfa-2b (12 KD) in the treatment of HCV genotype 1, 2 and 3 infections has been proven worldwide. Very little is known about sustained responses to HCV genotype 5, 6 and 10 treatment.

*Ribavirin*

The standard dose for combination therapy should be 1000 mg (2 tablets of 200 mg am and 3 tablets of 200 mg pm, daily for 24 or 48 weeks for patients of body weight ≤75 kgs and 1200 mg (3 tablets of 200 mg, am and 3 tabs of 200 mg pm daily) for patients of body weight > 75 kgs. A low dose RBV (800 mg daily) may be suitable for genotype 2 and 3 in combination therapy. However, for HCV genotype 4 a standard dose of 1000-1200 mg should be used.

*Pegylated-Interferon monotherapy*

The recommended dose regimen for HCV genotype 4 is 180 µg/week of PEG-IFN alfa-2a for 48 weeks as described above. For genotypes other than 4, both PEG-IFNs (alfa-2a and alfa-2b) may be used as described above.

**Postscript**

The jury wished to emphasize that these recommendations may have to be revised according to results of ongoing studies in KSA aimed at determining the efficacy and safety of PEG-IFN alfa-2b (12 KD). The optimal dose of PEG-IFN alfa-2b for the treatment of HCV genotype 4 will need to be addressed.

## DURATION OF TREATMENT

The optimal duration of treatment for genotype 4 and 1 is 48 weeks. Treatment should be stopped in patients who fail to show significant virological suppression at 12 weeks (<2 log reduction in viral load). This is because of the findings of the recently completed MOH PEG-IFN Clinical Trial suggesting that treated patients who did not show a viral suppression at week 12 failed to have an EOT response. Patients who show early viral clearance should be treated for a minimum of 48 weeks, except those with genotype 2 and 3 who can be treated for 24 weeks.

The dose of PEG-IFN and RBV should be adjusted according to the appendix 2 and 3 (for the management of side effects).

## MONITORING

*Treated patients.*

They should be monitored clinically, biochemically, and virologically at regular intervals. A reasonable schedule is presented in the chart (**Appendix 1**). It is essential to obtain virological RNA testing (preferably HCV-RNA quantification rather than HCV-RNA detection) at week 12, the result of which will be useful in the determination of an early response to therapy.

*Untreated patients.*

These persons can be classified in 2 major groups. Those who:

* Do not need IFN therapy (persistently normal ALT and normal/mild inflammation of the liver).
* These persons should be reevaluated at approximately yearly intervals and have regular alpha-fetoprotein, ALT and liver ultrasound.
* Are not eligible through established contraindications.
* The frequency of follow up will be defined by the contraindication.

## ADVERSE EVENTS

Combination therapy of PEG-IFN and RBV has a proven efficacy in the treatment of HCV infection. However, the safety and tolerability have to be cautiously evaluated through rigorous monitoring. The adverse effects of antiviral drugs are dose dependent and often reversible.

*Hematologic disorders.*

Hemolytic anemia mainly occurs in RBV treated patients. Rigorous monitoring of blood counts is indicated. Neutropenia and thrombocytopenia can occur during IFN therapy. Their management is described in **Appendix 2 and 3**.

*Psychiatric disorders.*

Psychiatric adverse events are among the most severe. Depression, psychosis, hallucinations and suicidal ideation have been reported with IFN therapy in patients with or without previous psychiatric disorders.

*Metabolic abnormalities.*

Thyroid abnormalities are frequent. Treatment should be discontinued in patients whose thyroid abnormalities cannot be controlled by medication. Diabetes and hypertriglyceridemia have been reported in patients treated with IFN.

*Cardiac disorders*

Impairment of cardiovascular functions, exacerbation of the symptoms of coronary artery disease, or both, may occur due to RBV-induced anemia. Interferon can aggravate other ischemic disorders. Close monitoring is recommended.

*Pulmonary disorders*

Dyspnea, interstitial pneumonitis and pneumonia have been reported in patients on IFN therapy.

*Ophthalmic disorders*

Visual defects such as retinal hemorrhages, retinal artery and vein occlusion were reported with IFN therapy. A visual examination prior to initiation of RBV is recommended in patients with diabetes and hypertension.

*Dermatologic effects*

Alopecia occurs with IFN. Rash, pruritus, cutaneous reactions (eczema, erythema, lichen planus, vitiligo) were reported in combination therapy of IFN and RBV.

**Managing adverse events**

Some adverse events can be managed without treatment interruptions. Flu-like symptoms (fever, chills, headache, myalgia) can be prevented by antipyretics. Other adverse events such as weight loss, fatigue, diarrhea and inflammation at the injection site can be well managed. Physicians and patients should be aware of major adverse events that may occur during therapy. Withdrawal or reduction of dosage of drugs may be indicated following the major adverse events. Up to 10% of treated patients, have serious adverse events that require cessation of therapy. In our clinical trial, 12 out of 180 HCV genotype 4 patients had to be withdrawn from treatment because of major adverse events. Reintroduction of therapy can be considered only after careful and informed consent of the risks by the physician and the patient for dose reduction strategy or withdrawal (see **Appendix 2 and 3**).

## COUNSELING

It is essential that patients who are infected by HCV are counseled adequately to alleviate their anxiety, improve their understanding of the infection and disease, and provide motivation for complying with doctor's advice. Doctors and caregivers involved in counseling must avail themselves with the best and latest information on the subject.

Pretreatment counseling must include discussions about the natural history, the available drugs for treatment, the side effects, the investigations that are necessary for proper assessment and treatment. In addition to verbal

counseling, a leaflet summarizing the aforementioned information may be provided to the patients and their relatives where indicated. The counseling sessions must be documented in the patient's records.

Patients who are not eligible or suitable for treatments, or who do not "require" treatment (by current standards) must receive an adequate explanation and counseling with particular attention to the basis for holding treatment. This will prevent unnecessary "shopping around" for therapy.

Failed therapy may be depressing to patients; careful support must therefore be provided. Alternative drug therapy may be discussed with the patient. Information on long term monitoring should be part of the counseling.

## MONITORING OF TREATMENT IN NON-GOVERNMENTAL HOSPITALS

It is recommended that the consensus statement and guidelines should be made available to non-governmental hospitals, with the advice that treating doctors should adhere to the principles of management contained therein. It will be useful to design a strategy by which treatment of HCV in these hospitals can be monitored continually. A voluntary registration of such cases is strongly recommended.

## LIVER TRANSPLANTATION PROGRAM

Those who have advanced liver diseases, or who have progressive disease following failure of therapy will continue to receive other forms of management for their disease. Clearly many will need and benefit from liver transplantation. Therefore, it is essential that the liver transplantation programs in Saudi Arabia are strengthened and expanded to accommodate these cases.

## LABORATORY SUPPORT (GENERAL PATHOLOGY AND VIROLOGY)

Hepatitis C virus infection represents a major health problem for the Kingdom. The investigation of patients, their monitoring during therapy and the cost of drugs represent a significant financial investment for the country. To provide a secure and sustainable base on which to run this program it will be necessary to ensure that staff and equipment in a molecular-based laboratory are of sufficient quality and number to provide the viral testing required.

Detection of HCV-RNA and its measurement is not simple, being based upon a multi-component and multi-step assay. Proficiency in the handling of RNA extraction, the RNA itself and the running of amplification assays requires trained and motivated staff as well as expensive and dedicated equipment. These attributes are absolutely necessary for the delivery of a reliable service. It is recommended that resources are identified and provided for a central testing and reference unit, which is capable of delivering the testing required in a safe, accurate and timely manner.

The unit should be able to run the commercial assays for the purpose of the program and it should also develop its skills to the point that it may be able to:

* sustain its own in-house training program for staff,
* develop its in-house reagents,
* develop expertise in molecular diagnostics in and beyond the field of HCV.

## DRUG SUPPLY

Drugs should be regularly supplied to hospitals, and this activity should be sustained to avoid any disruption, which may hamper the management and the monitoring of patients.

## FUTURE CHALLENGES AND RESEARCH

Major research has been carried out in the KSA especially in relation to HCV genotype 4. However, many issues of national and international concern remain to be resolved.

Despite the availability of IFN and RBV for treatment, the response to therapy remains unsatisfactory. This is due to the relatively low efficacy in the treatment of some specific genotypes [genotype 1 and 4], the high frequency of side effects, the high cost of the drugs and the patient's adherence to treatment schedules. The challenge is to develop and produce drugs with higher efficacy, less toxicity and with oral bioavailability. The results of clinical trials involving newer drugs are awaited.

The Kingdom of Saudi Arabia has led the field in the treatment of HCV genotype 4 infections. Further valuable data (including the description of the spectrum of disease found at presentation) will come from a collation of the results of the ongoing clinical trials. The observations from these studies and those arising from this intervention will be useful and valuable to other countries with similar profiles of viral genotype.

Hepatitis B virus and HCV co-infections are not uncommon in the Saudi population, particularly in those with CLDs. This provides an opportunity to investigate the effect of dual infection upon the severity and progression of liver pathology. Does co-infection reduce the likelihood of success to treatment of HCV? Does HCV impact upon the treatment of HBV with anti-viral drugs? What is the interrelationship of the 2 viruses at the molecular level? Studies could define if there is viral interference and any effect upon evolution of the viruses in-vivo.

The virological diagnosis has evolved from serological testing to nucleic acid techniques, which are more complex and expensive to perform. It is envisaged that strategies to reduce the cost, and complexity will be put in place. This includes the preparation of in-house reagents. Training of staff and continuing technical education is mandatory.

The need for secure virological services for this intervention also provides an opportunity to develop molecular virology expertise on the back of this need. The methods which are required for the provision of HCV genotyping and RNA quantification are also applicable to other agents such as hepatitis B and to other situations such as outbreaks of other exotic agents such as Rift Valley or other flaviviruses. The development of a greater expertise in this methodology would be of considerable value beyond that of just hepatitis viruses.

There are limited studies in KSA concerning the identification of risk factors and mode of transmission of HCV. Studies indicated that the rates of perinatal and intra-familial transmission are low. The results of family and transmission studies on a larger population would be informative and provide the basis on which to recommend the use of vaccine if or when it becomes available.

The high prevalence of HCV infection in hemodialysis units is a major problem and should be addressed. Studies should be conducted to determine the natural history of HCV, particularly genotype 4, in these patients.

The determination of the most effective control measures that will contain the risk of transmission is essential. Few similar situations are known globally, and data from the KSA will be useful to other countries.

Studies on the phylogenetics of HCV 4 in the country need to be undertaken. It is not known how similar is the genotype 4 in Saudi patients to that seen in patients of neighboring countries nor is it known, the diversity of this virus in KSA. Hepatitis C virus genotype 4 phylogenetic data may help in understanding where and when that infection arose. It could also provide information on the rate of viral evolution.

In conclusion, treatment with PEG-IFN combined with RBV is currently considered to be the cost effective therapy of acute and chronic hepatitis C infection. The role of this combination in the treatment of HCV-PCR positive patients with constantly normal liver enzymes or with only minimal inflammation and fibrosis on liver biopsy is still to be determined. It is hoped that this consensus guideline will be helpful to physicians treating patients with hepatitis C infection and be a tool for unifying the treatment of this disease in Saudi Arabia.

# Appendix 1

## Patient's laboratory monitoring sheet

Name: Nationality:

Sex: Hospital number:

Age: Phone [office/residence]:

| Weeks | 0 | 1 | 2 | 3 | 4 | 6 | 8 | 12 | 18 | 24 | 30 | 36 | 48 | 56 | 64 | 72 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Virology*** | | | | | | | | | | | | | | | | |
| HCV-RNA [qualitative] | | | | | | | | | | | | | x | | | x |
| HCV-RNA [quantitative] | x | | | | | | | x | | | | | | | | |
| HCV genotyping | x | | | | | | | | | | | | | | | |
| ***Histology*** | x | | | | | | | | | | | | | | | x |
| ***Biochemistry*** | | | | | | | | | | | | | | | | |
| ALT | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| AST | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Total Bilirubin | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Alk.phosphatase | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| ***Kidney Test*** | | | | | | | | | | | | | | | | |
| Urea | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Creatinine | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Na/K | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| ***Thyroid Test*** | | | | | | | | | | | | | | | | |
| TSH | x | | | | | | | | | x | | | | | | x |
| T3 | x | | | | | | | | | x | | | | | | x |
| Free T4 | x | | | | | | | | | x | | | | | | x |
| ***Urinalysis*** | x | | | | | | | | | x | | | | | | x |
| ***Hematology*** | | | | | | | | | | | | | | | | |
| WBC | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| ABC | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Hb | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Hct | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| CMV | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| MCH | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| AN | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Platelets | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Reticulocyte | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| PT/Control | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| PTT/Control | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| α−Fetoprotein | x | | | | | | | | | x | | | x | | | |
| Pregnancy test [urine or serum] | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |

HCV-RNA - hepatitis C virus - ribonucleic acid, ALT - alanine aminotransferase, AST - aspartate aminotransferase, Alk. - alkaline, Na/K - sodium/potassium, TSH - thyroid stimulating hormone, T3 - triiodothyronine, T4 - thyroxine, WBC - white blood cell, RBC - red blood cell, Hb - hemoglobin, Hct - hematocrit, MCV - mean corpuscular volume, MCH - mean corpuscular hemoglobin, ANC - absolute neutrophil count, PT - prothrombin time, PTT - partial thromboplastin time

# Appendix 2

## Dose reduction chart

**Pegylated interferon alfa-2a (180µg) dose adjustment guidelines for serum alanine aminotransferase (ALT) (U/L).**

| Baseline serum (ALT) | On-treatment serum (ALT) | Downward dose adjustment |
|---|---|---|
| ≤100 | <200 | Continue to treat with 180µg PEG-IFN alfa-2a |
| Start with 180µg PEG-IFN alfa-2a | 200-300 | Repeat test in one week. If ALT decreased or stable (≤10% increase), continue PEG-IFN at 180µg and follow up every 1-2 weeks to assure stability. If increase by >10% reduce dose to 135µg and follow with weekly testing until ALT stabilize or decrease. |
| | 301-500 | Repeat serum ALT. If ALT decrease or stabilize (≤10% increase), reduce PEG-IFN alfa-2b dose to 135µg and follow weekly to assure stability. If increased by >10%, withdraw PEG-IFN until ALT decreases to <300 then resume treatment at 90µg. Follow up every 1-2 weeks until ALT stabilize. If a further 10% increase occurs stop treatment. |
| | >500 | Stop treatment until ALT decreases to <300 then resume PEG-IFN alfa-2a at 90µg and follow up every 1-2 weeks. If ALT >300 stop treatment. |
| 101-200 | ≤300 | Continue to treat with 180µg PEG-IFN alfa-2a. |
| Start with 180µg PEG-IFN alfa-2a | 301-500 | Repeat serum ALT. If ALT decrease or stabilized (≤10% increase) reduce PEG-IFN alfa-2a to 135µg. Check ALT weekly to assure stability. If increased by >10%, stop treatment until ALT decreases to <300 then resume treatment at 90µg. Follow every 1-2 weeks until ALT stabilize. If a further 10% increase occurs stop treatment. |
| | >500 | Stop treatment until ALT decreased to <300 then resume test drug at 90µg and follow every 1-2 weeks. If ALT >300, stop test drug. |
| 201-300 | ≤400 | Continue to treat with 180µg PEG-IFN alfa-2a |
| Start with 180µg PEG-IFN alfa-2a | 401-500 | Repeat serum ALT. If ALT decrease or stabilize (≤10% increase), reduce PEG-IFN to 135µg and follow weekly to assure stability. If increased by >10%, hold dose until ALT decreases to <300 then resume test drug at 90µg and follow every 1-2 weeks until stable. If a further 10% increase occurs, stop treatment. |
| | >500 | Stop treatment until ALT decreased to <300 then resume test drug at 90µg and follow every 1-2 weeks. If ALT >300, stop treatment. |
| 301-500 | ≤500 | Continue to treat with 180µg PEG-IFN alfa-2a. |
| Start with 18µg PEG-IFN alfa-2a | >500 | Repeat serum ALT. If ALT decreased or stabilize (≤10% increase), reduce PEG-IFN to 135µg and follow weekly to assure stability. If increased by 10%, stop treatment until ALT decreases to less than baseline then resume PEG-IFN alfa-2a at 90µg and follow every 1-2 weeks until stable. If a further 10% increase occurs stop treatment. |
| >500 | ≤25% increase | Continue to treat with 180µg PEG-IFN alfa-2a. |
| Start with 180µg PEG-IFN alfa-2a | >25% increase | Repeat serum ALT. If ALT decrease or stabilize (≤10% increase), reduce PEG-IFN to 135µg and follow weekly to assure stability. If increased by >10%, stop treatment until ALT decreases to less than baseline then resume treatment at 90µg. Follow up every 1-2 weeks until serum ALT stabilizes. If a further 10% increase occurs stop treatment. |

## *Continuation of appendix 2*

**Dose adjustment of PEG-IFN alfa-2a for hematological indices**

Absolute neutrophil count (cells/mm$^3$)

| Parameter cells/mm$^3$ | Time | Downward dose adjustment |
|---|---|---|
| ≥1000 | Week 0 | Treat with 180µg PEG-IFN alfa-2a |
| <1000 but >750 | Week 1-2 | Reduce to 135µg PEG-IFN alfa-2a |
| | Week 3-48 | Continue to treat with 180µg PEG-IFN alfa-2a |
| <750 but >500 | Week 1-2 | Stop treatment until ≥750 cells/mm$^3$ then resume dose with 135µg PEG-IFN alfa-2a |
| | Week 3-48 | Reduce to 135µg PEG-IFN alfa-2a |
| <500 but >250 | Week 1-2 | Stop treatment until ≥750 cells/mm$^3$ then resume dose with 90µg PEG-IFN alfa-2a |
| | Week 3-48 | Stop treatment until ≥750 cells/mm$^3$ then resume dose with 135µg PEG-IFN alfa-2a |
| <250 | | Stop treatment. |

Platelets count (cells/mm$^3$)

| Parameter cells/mm$^3$ | Downward dose adjustment |
|---|---|
| ≥50,000 | Treat with 180µg PEG-IFN alfa-2a |
| <50,000 but >35,000 | Stop treatment until ≥50,000 cells/mm$^3$ then resume dose with 135µg |
| <35,000 but >25,000 | Stop treatment until >50,000 cells/mm$^3$ then resume dose with 90µg |
| <25,000 | Stop treatment. |

PEG-IFN -pegylated interferon

# *Appendix 3*
# *Guidelines of PEG-IFN alfa-2b dose modification*

Dose adjustment of PEG-IFN alfa-2b (cells/mm$^3$)

| **Platelet count** | **Dose adjustment** |
|---|---|
| >50 x $10^9$/L | Treat with PEG-IFN alfa-2b 1.5 mcg/kg body weight |
| <50 - 25 x $10^9$/L | Dose reduction for PEG-IFN alfa-2b |
| <25 x $10^9$/L | Stop treatment |

Dose adjustment of PEG-IFN alfa-2b for white blood cell count

| **White blood cell count** | **Dose adjustment** |
|---|---|
| >1.5 x $10^9$/L | Treat with PEG-IFN alfa-2b 1.5 mcg/kg body weight |
| <1.5 - 1.0 x $10^9$/L | Dose reduction for PEG-IFN alfa-2b |
| <1.0 x $10^9$/L | Stop treatment |

Dose adjustment of PEG-IFN alfa-2b for granulocyte count

| **Granulocyte count** | **Dose adjustment** |
|---|---|
| >0.75 x $10^9$/L | Treat with PEG-IFN alfa-2b 1.5 mcg/kg body weight |
| <0.75 - 0.5 x $10^9$/L | Dose reduction for PEG-IFN alfa-2b |
| <0.5 x $10^9$/L | Stop treatment |

Dose adjustment of PEG-IFN alfa-2b for biochemical parameters

| **Parameter** | **Dose adjustment** |
|---|---|
| ALT / AST (2 x baseline and >10 x ULN | Stop treatment |
| Creatinine (>2.0 mg/dL or >176.8 umol/L) | Stop treatment |
| Bilirubin-direct ( >2.5 x ULN) | Stop treatment |
| Bilirubin-indirect ( >4 mg/dL or [>68.4 µmol/L for > 4 weeks]) | Stop treatment |

*PEG-IFN alfa-2b dose reduction according to the initial dose given

| **Initial PEG-IFN alfa-2b dose (µg; QW)** | **First dose reduction (µg; QW)** | **Second dose reduction (µg; QW)** |
|---|---|---|
| 80 | 50 | Stop treatment |
| 100 | 80 | 50 |
| 120 | 80 | 50 |
| 150 | 100 | 80 |

*The dose reduction differs according to the initial dose of PEG-IFN alfa-2b which is based on body weight.

Dose adjustment of ribavirin for hemoglobin

| Hemoglobin | Time | **Downward dose adjustment** |
|---|---|---|
| Normal hemoglobin >12gms/dl for males >10gms/dl for females | Week 0 | Treat with 1000-1200mgs ribavirin daily according to body weight |
| <10gms/dl but >8.5gms/dl for both sexes | Week 1-4 | Reduce dose to 800mgs - 1000 mgs/day. If Hgb normalize, increase dosage to 1000-12000 mgs/day |
| | Week 5-48 | - as above - |
| <8.5gms/dl | Week 4-48 | Stop treatment |

PEG-IFN - pegylated interferon, ALT - alanine aminotransferase, AST - aspartate transaminase, QW - once weekly, ULN - upper limit of normal