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Consensus conference

Treatment of hepatitis C

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FOREWORD

This conference was organized according to the methodological rules published by the Agence Nationale d'Accréditation et d'Évaluation en Santé (ANAES). *The conclusions and recommendations contained in this document were written, in full independence, by the jury of the conference. ANAES is in no way accountable for these views.*

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Questions asked to the jury

Question 1

Which patients should be treated?

Question 2

What are the most appropriate investigations before treatment?

Question 3

What is the optimal treatment?

Question 4

How to monitor treated patients?

Question 5

How to monitor untreated patients?

Major advances have been made in recent years in our knowledge of the epidemiology of hepatitis C virus (HCV) infection, and in patient management.

In two large studies, the prevalence of anti-HCV antibodies among French adults was found to be 1.1 and 1.2%. Eighty percent of these subjects being viremic, it was estimated that between 400,000 and 500,000 people living in France had chronic HCV infection. However, large variations are found among different subpopulations. The prevalence of HCV infection is approximately 60% among intravenous drug users and 25% in subjects infected by human immunodeficiency virus (HIV). Thus, between 25,000 and 30,000 subjects are thought to be coinfected by HCV and HIV. The rate of HCV infection among prison inmates is thought to be at least 25%.

Screening promotion campaigns have led to a marked increase in the proportion of HCV-infected persons who are aware of their serological status. Most diagnoses are made in patients who were infected years previously, and their number in no way reflects the rate of new infections, i.e. the current incidence of HCV infection. The latter is not precisely known, but the estimated yearly incidence of new infections in France is about 5,000, of which 70% would be associated with intravenous drug use.

Surveys conducted during the last decade have shown marked changes in the characteristics of diagnosed patients:

- Among newly diagnosed patients, the proportion of those with mild chronic hepatitis has increased, leading to a corresponding fall in the proportion of patients with cirrhosis.
- As a large proportion of patients was infected several decades ago, the absolute number of severe cases, i.e. cirrhosis and hepatocellular carcinoma, is increasing.
- The modes of HCV transmission have evolved, with a gradual reduction in the proportion of cases related to transfusion and an increase in those related to intravenous drug use. These changes also largely account for the observed changes in the HCV genotype profile, with an increase in the prevalence of genotype 3 (correlated with an improvement in treatment response rate).

Public health campaigns conducted in recent years have therefore created a paradox: newly diagnosed patients have less severe disease and are therefore less likely to require treatment, while the likelihood of their response to treatment has increased.

Since the first French consensus conference on hepatitis C, held in 1997, major advances have been made in therapeutic approaches, virological methods, and our knowledge of the natural history of HCV infection.

The percentage of patients who experience a sustained virological response to treatment has risen from about 10% with interferon (IFN) monotherapy to more than 50% with treatment combining pegylated IFN (PEG IFN) and ribavirin. Thus, HCV infection can now be eradicated in more than 50% of patients, albeit with a risk of noteworthy adverse effects. Several studies have identified factors predictive of a good response to treatment, such as young age, female gender and, especially, infection by HCV genotype 2 or 3 (response rate of about 80% in clinical trials).

Many studies on the natural history of HCV infection indicate that the clinical course is usually mild. However, these studies involved subjects infected early in life, and follow-up is probably too short to rule out a risk of more severe disease in the long term. Indeed, some studies suggest that fibrosis may accelerate after age 50 to 60 years.

The information provided to HCV-infected patients has considerably improved in recent years, thanks in particular to patient associations. Some patients may wish to see their infection cured, even if they have little, if any, liver damage. As a result, the treatment target is tending to shift from the clinical disease itself (i.e. the hepatic lesions of chronic hepatitis C) to the underlying viral infection. This change might have a significant impact on the indications of pretreatment investigations, especially liver biopsy.

Some patients have extensive fibrosis or cirrhosis at diagnosis. When treatment fails to induce a virological response, the question arises as to the need for “maintenance” treatment aimed at limiting the progression of fibrosis and the risk of hepatocellular carcinoma, even though there is no high-level scientific evidence for the efficacy of such treatment. Several factors are associated with more rapid progression of fibrosis, including male gender, infection at an advanced age, excessive alcohol consumption, and HCV-HIV coinfection. Excessive alcohol consumption and active intravenous drug use have previously been considered as relative contraindications to treatment. The prognosis and management of intravenous drug users and HCV-HIV coinfected patients, who represent the bulk of newly diagnosed cases, has improved with the introduction of substitution therapy and advances in antiretroviral therapy. These advances call for a change in patient management towards a more community-based holistic approach.

With the aim of assessing these changes and optimizing the management strategy for HCV-infected patients, a new consensus conference was held in Paris on 27 and 28 February 2002.

It is likely that some of the consensus recommendations will have to be revised in the more or less short term as the results of ongoing studies become available. The recommendations will also have to be evaluated from the cost-effectiveness standpoint. They should help to improve the therapeutic management of HCV infection and access to care that are two major objectives of the new French government's campaign against hepatitis C launched in February 2002.

QUESTION 1. WHICH PATIENTS SHOULD BE TREATED?

Only adults with chronic hepatitis C confirmed by the presence of HCV RNA in serum qualify for treatment. Treatment indications are based on histological assessment of hepatic lesions, but must also take into account individual factors (quality of life, age, comorbidity, extrahepatic manifestations, etc.) and virological factors, which influence the risk-benefit ratio of treatment.

The motivation of the patient and family/friends must be carefully assessed before starting treatment. This is an important element for the success of treatment and must be given sufficient time.

1. General therapeutic indications

The severity of chronic hepatitis C is mainly defined by the stage of fibrosis. The grade of histological activity must also be taken into account in the decision to treat. The first aim of treatment is to eradicate the virus, i.e. to cure the infection. The second objective is to prevent, stabilize or even improve hepatic lesions.

1.1. Patients with moderate or severe chronic hepatitis (F2 or F3)

Chronic hepatitis with fibrosis stage F2 or F3 with the METAVIR scoring system is a recognized indication for treatment, whatever the grade of necroinflammatory activity (see question 2, §2.6. liver biopsy).

1.2. Patients with cirrhosis (F4)

In patients with cirrhosis (stage F4 with the METAVIR scoring system), the aim of the treatment is not only to obtain a sustained virological response but also to stabilize the disease and to avoid its major complications, including hepatocellular carcinoma. The decrease of the incidence of complications appears to be related with a sustained virological or biochemical response. After initial treatment, if no virological response is obtained, IFN "maintenance" therapy (an off-licence indication in France) can be proposed in an attempt to reduce disease progression. This treatment can be envisaged only in patients with a biochemical response (normalization or marked reduction of transaminase levels) at the end of the initial treatment. The same approach can be recommended for patients with fibrosis stage F3. However, the efficacy of this strategy remains to be validated, and these patients must, whenever possible, be enrolled in clinical trials.

Antiviral treatment is contraindicated in patients with "decompensated" cirrhosis.

1.3. Patients with mild chronic hepatitis (F0 or F1) or chronic hepatitis associated with normal transaminase levels

Classically dealt with separately, these two situations in fact raise similar issues. In the absence of aggravating factors (obesity, excessive alcohol consumption, HCV-HIV coinfection, etc.), the risk of progression is low and the long-term benefits of treatment are not established, especially in patients with normal transaminase levels. Simple monitoring, without treatment, is therefore recommended. Long-term studies of the benefits of treatment are necessary.

Nevertheless, treatment may be envisaged for patients with extra-hepatic manifestations (in particular vasculitis) and those who are highly motivated (an off-license indication in France), especially when the HCV genotype is 2 or 3.

1.4. Patients who relapse or do not respond

Relapse is defined as the recurrence of detectable serum HCV RNA within 6 months post-treatment in a patient who was serum HCV RNA negative at the end of treatment. *Non response* is defined as the persistence of detectable serum HCV RNA at the end of treatment.

Combined therapy with PEG IFN and ribavirin (by analogy to combination therapy with standard IFN and ribavirin) must be offered to patients who relapsed after IFN monotherapy. There are insufficient data on which to base the decision to treat patients who relapsed after combination therapy with standard or PEG IFN. Patients with severe disease (F3 or F4) may be offered IFN "maintenance" therapy.

Patients who did not respond to IFN monotherapy can be treated by combination therapy with PEG IFN and ribavirin, although the efficacy of this treatment remains to be validated. No definite strategy is available for patients who did not respond to combination therapy with standard IFN or PEG IFN and ribavirin.

1.5. Liver transplant patients

HCV infection almost always relapses after liver transplantation for HCV-related cirrhosis or hepatocellular carcinoma. High viral load, onset of symptomatic hepatitis, and strong immunosuppression appear to be factors of poor prognosis, warranting enrollment in ongoing clinical trials.

1.6. Patients with acute infection

The diagnosis should be ideally made at an early stage, within weeks of infection, by the detection of serum HCV RNA in two successive samples. If acute infection is confirmed (with or without acute hepatitis), treatment usually avoids chronicity. This strategy applies particularly to subjects who are accidentally exposed to potentially infected body fluids.

2. Influence of individual factors

2.1. Chronic excessive alcohol intake

Chronic excessive alcohol intake seems to be associated with an increase in HCV replication and leads to more rapid and more frequent development of cirrhosis. Efficacy, tolerability and adherence of antiviral treatment are lower in patients with excessive alcohol consumption. An attempt should be made to wean the patient for at least 6 months before starting treatment, or at least to obtain a maximal reduction in alcohol consumption.

2.2. Drug use

HCV infection acquired through intravenous or nasal drug use is associated with a number of favorable characteristics. Diagnosis and management generally occur at a relatively young age, the duration of infection is relatively short, histological lesions are usually mild, and the prevalence of genotype 3 is high.

On the other hand, some factors frequently associated with active intravenous drug use worsen the prognosis of HCV infection, such as excessive alcohol consumption, concomitant HIV or hepatitis B virus (HBV) infection, psychiatric disorders, and social precariousness.

Given the higher frequency of factors favoring a satisfactory virological response, the therapeutic indications should be broader in active intravenous drug users. These patients should be taken in charge by a multidisciplinary team before starting treatment, in order to evaluate their psychological, relational and social stability (often favored by substitution therapy), psychotropic drug use and the need for psychological support, and to provide them and their friends/family with adequate information.

Occasional intravenous drug use by an otherwise stabilized patient does not contraindicate treatment.

2.3. Psychiatric disorders

For patients with psychiatric disorders, it seems reasonable to offer anti-HCV treatment only to those with severe liver disease, and provided that psychiatric stabilization can be achieved. This is because treatment can provoke or worsen serious psychiatric disorders.

It is crucial to provide the patient and friends/family with adequate information, especially on the risk of severe depression. A preliminary psychiatric assessment and close follow-up are necessary. Antidepressant prophylaxis may be warranted for patients with a relevant history.

2.4. HIV-HCV coinfection

HIV-HCV coinfection is associated with more severe histological lesions and with more frequent and more rapid progression to cirrhosis. In these patients, the decision to treat HCV infection will depend mainly on the results of liver biopsy.

In coinfected patients with moderate to severe histological lesions, it may be difficult to decide which infection should be treated as a priority.

Several situations can arise:

- In immunocompetent coinfected patients with no immediate indication for antiretroviral treatment, HCV infection should be treated first; the absence of antiretroviral treatment is likely to facilitate adherence to anti-HCV therapy and to improve its efficacy. Above all, it avoids the risk of interactions between ribavirin and other nucleoside analogs, and a potentiation of antiretroviral hepatotoxicity by the underlying liver disease;
- In coinfected patients who are already receiving antiretroviral treatment, the indication of anti-HCV treatment is based on the same histological criteria as in patients without HIV coinfection; particular attention is given to the risks related to the combination ribavirin/anti-HIV nucleoside analogs;
- Anti-HCV treatment is not the priority in the immunodepressed patient; severe immunodepression seems to be associated with a poorer virological response to anti-HCV treatment and with poorer tolerability.

2.5. Other intercurrent disorders

- Constitutional clotting disorders (mainly hemophilia) do not modify the treatment modalities.

- In thalassemic patients, iron overload induced by dyserythropoiesis and multiple transfusions worsens the liver disease and may reduce the efficacy of IFN. Ribavirin is generally contraindicated by the increased risk of severe hemolysis. Depending on histological findings, treatment with IFN may be justified. Provided monitoring is reinforced, combination therapy can be offered to IFN non-responders, even though transfusion requirements may increase.

- In non-dialysed patients with renal failure, IFN and ribavirin are usually contraindicated. In dialysed patients, histological examination is crucial, especially to detect cirrhosis, as this is a contraindication of kidney transplantation on its own. Interferon is indicated in this setting, despite its poor tolerance, as it seems to induce a sustained virological response and histological improvement more often than in non-dialysed HCV-infected patients. HCV infection should be treated before envisaging renal transplantation, which contraindicates the use of IFN.

2.6. Children

The mid-term outcome of vertically infected children is usually good. Treatment indications are rare (and off-licence indication in France) and must be determined in specialized centers. Children should be treated within clinical trials.

2.7. The elderly

Age-related comorbidities must be taken into account in the decision to treat. Treatment is generally less well tolerated. These factors do not formally contraindicate the treatment of HCV infection in elderly patients.

QUESTION 2. WHAT ARE THE MOST APPROPRIATE INVESTIGATIONS BEFORE TREATMENT?

When anti-HCV antibodies are detected in two consecutive samples with two different reagents, it is crucial to test for viral replication by the detection of HCV RNA in serum by qualitative assay.

The absence of detectable HCV RNA in serum (20 to 25% of subjects) shows that HCV infection has resolved. If serum transaminase level is normal, no further investigation is necessary. If serum transaminase level is increased, another cause must be looked for.

The presence of detectable serum HCV RNA (75 to 80% of subjects) demonstrates chronic HCV infection. First, a clinical assessment is performed, then investigations are conducted to assess whether treatment is indicated.

1. Clinical assessment

The following background information must be collected before conducting further investigations:

- Age, gender, sociofamilial context;
- personal history, especially of thyroid disorder, neuropsychiatric disorder (epilepsy, depression, etc.), autoimmune disorder, etc.;
- presumed date and mode of infection;
- former or current drug addiction;
- ongoing treatments (contraceptive, psychotropic, antihypertensive, oral antidiabetic and lipid-lowering drugs);
- hepatitis A and B vaccination status.

Clinical assessment should include a search for extrahepatic disorders possibly linked to HCV infection (fatigue, arthralgia, myalgia, cutaneous signs), physical signs of cirrhosis (hepatomegaly, manifestations of hepatocellular insufficiency or portal hypertension) and signs of comorbidity (high body mass index, excessive alcohol consumption).

2. The treatment decision process

Arguments for and against antiviral treatment are taken into account.

2.1. **Laboratory investigations** include liver tests (transaminase, gammaglutamyl transpeptidase, alkaline phosphatase, bilirubin, prothrombin time) and hemogram.

An increase in transaminase level, despite not being strictly correlated with histological lesions, may suggest a progressive disease that warrants treatment. In contrast, normal transaminase level is generally associated with a slow or absent disease progression. Normality of transaminase levels must be confirmed each month for 6 months. Immunodepression can be associated with normal transaminase levels, even in patients with severe liver disease.

2.2. It is crucial to determine the **HCV genotype**. The genotype influences the indication for treatment, the pretreatment assessment, and the therapeutic strategy itself. Indeed, current treatments are shorter and more effective in patients with genotype 2 or 3 infection.

2.3. **HCV RNA levels**, determined in serum by molecular techniques, do not correlate with the severity of hepatic lesions but is predictive of the response to treatment. Its measurement before treatment provides a baseline value to appreciate the early response to treatment (validated for HCV genotype 1 infection). Quantification of HCV core antigen (HCV antigenemia, not available at the time of the conference) is less costly and could replace molecular techniques when viral load is high (the current assay has low sensitivity).

2.4. The **search for comorbidity** should include:

- HIV serology (and, if positive, a CD4 cell count);
- HBV serology;
- Thyroid-stimulating hormone (TSH) assay and detection of antithyroperoxidase autoantibodies;
- detection of anti-nuclear, anti-smooth muscle and anti-LKM1 autoantibodies;
- creatininemia and proteinuria;
- glycemia and lipid profile;
- ferritin level and transferrin saturation coefficient.

2.5. **Abdominal sonography** is performed to examine the liver parenchyma and to detect signs of portal hypertension.

2.6. **Liver biopsy** is performed to assess the degree of hepatic lesions.
It is usually done by the transparietal route, the transjugular route being reserved for patients with clotting disorders and those on dialysis.

For optimal interpretation, a sample of at least 10 mm comprising at least 6 portal spaces is required. The grade of necroinflammation (scored from A0 to A3) and the stage of fibrosis (scored from F0 to F4) compose the METAVIR score, which is more relevant than the Knodell score in chronic hepatitis C.

. *Indications*

♦ Liver biopsy is crucial in most cases, because the stage of fibrosis is the key parameter for prognosis and therapeutic decision-making.

♦ Liver biopsy may not be necessary if the decision to treat has already been taken and does not depend on the histological result, i.e:

- when the aim of the treatment is viral eradication, independently of histological lesions; this occurs in the case of:
  - infection by HCV genotype 2 or 3, in the absence of comorbidity (excessive alcohol consumption, HCV-HIV coinfection, renal failure), because treatment efficacy is approximately 80% in clinical trials;
  - women planning to become pregnant and wishing to avoid the (low) risk of transmitting the virus to their child;
  - symptomatic cryoglobulinemia (viral eradication is crucial for the control of symptoms);
  - HCV-HIV coinfection, when antiretroviral treatment can be postponed: primary treatment of HCV infection reduces the risk of antiretroviral

hepatotoxicity and avoids interference between the drugs used for the two infections.

- when a combination of clinical, biological and sonographic signs clearly shows the presence of cirrhosis.

♦ Liver biopsy is not required if antiviral treatment is not indicated in the short term. This is especially the case of patients with "decompensated" cirrhosis and those with both repeatedly normal transaminase levels and no comorbidity.

2.7. **Serum markers of fibrosis** might become an alternative to liver biopsy if they are validated in ongoing studies.

2.8. Additional investigations are necessary to determine **permanent or temporary contraindications to treatment**:

- pregnancy test;
- electrocardiogram for patients over 50 and those with known heart disease;
- ophthalmologic examination for patients with risk factors;
- psychiatric evaluation (crucial for patients with a history of psychiatric disorders).

QUESTION 3. WHAT IS THE OPTIMAL TREATMENT?

Treatments for HCV infection include antiviral drugs, liver transplantation and supportive measures.

1. Antiviral treatments

Antiviral treatment options include standard IFN, combination of standard IFN + ribavirin and, more recently, combination of PEG IFN + ribavirin.

PEG IFN is standard IFN conjugated to polyethylene glycol (PEG). Pegylation of IFN leads to a reduced renal clearance, a longer half-life, and a prolonged plasma concentration of the drug, permitting a single weekly injection.

1.1. PEG IFN + ribavirin combination therapy: the reference treatment

There are two type of PEG IFN: α-2a and α-2b.

Two recent randomized controlled trials involving more than 2,500 patients compared PEG IFN + ribavirin and IFN + ribavirin. The two studies gave close results in terms of sustained virological response. The most effective treatment regimens compared with standard combination therapy were as follows:

- PEG IFN α-2b (1.5 µg/kg/week) + ribavirin (800 mg/d);
- PEG IFN α-2a (180 µg/week) + ribavirin (1,000 to 1,200 mg/d according to body weight).

One of these studies showed that, in patients infected by HCV genotype 1, the decline in viral load at 12 weeks was predictive of a sustained virological response.

In the trial of PEG IFN α-2b, a retrospective analysis showed that the rate of sustained virological response was higher in the subgroup of patients who received ribavirin doses > 10.6 mg/kg/d. This subsequently formed the basis for adjustment of the ribavirin dose to body weight.

Treatment lasted 48 weeks in both trials. However, with the standard IFN + ribavirin combination, the French recommended treatment duration (according to the licensing terms) for patients with HCV genotype 2 or 3 infection is 24 weeks. By analogy, a treatment duration of 24 weeks for PEG IFN + ribavirin treatment can be proposed for patients infected by HCV genotype 2 or 3.

The jury recommends:

♦ One of the following two regimens:

- PEG IFN α-2b (1.5 µg/kg/week) + ribavirin (800 mg/d below 65 kg, 1,000 mg between 65 and 85 kg, and 1,200 mg beyond 85 kg);
- PEG IFN α-2a (not available for use outside of therapeutic trials at the time of the consensus conference) (180 µg/week) + ribavirin (800 mg/d below 65 kg, 1,000 mg between 65 and 85 kg, and 1,200 mg beyond 85 kg).

♦ The duration of treatment depending on the HCV genotype:

- 48 weeks for patients infected by genotype 1, if viral load after 12 weeks of treatment is undetectable or has fallen by more than 2 log relative to baseline. If this

endpoint is not reached, the treatment can be stopped if the objective is viral eradication, because the likelihood of treatment failure is high. If the objective is to reduce the progression of hepatic lesions, treatment can be maintained in the event of biochemical response;
- 24 weeks for patients infected by genotype 2 or 3, by analogy with IFN + ribavirin combination therapy and pending the results of ongoing trials;
- For patients infected by genotype 4, which is little sensitive to treatment, as genotype 1, it has not yet been demonstrated that a decline in viral load of less than 2 log at 12 weeks is predictive of treatment failure. A 48-week treatment duration can thus be proposed, depending on the individual risk-benefit ratio. Although specific data are lacking, the same regimen can be proposed for genotype 5 or 6 infection.

The jury underlines that these recommendations may have to be revised according to the results of ongoing or future studies aimed at determining:
- The optimal dose of PEG IFN: the same efficacy of 1.5 µg/kg/week and 1 µg/kg/week PEG IFN α-2b monotherapy in terms of sustained virological response, and the high incidence of adverse effects with high doses, stress the need for trials of combination therapy with a dose of 1 µg/kg/week;
- The optimal dose of ribavirin: the current dose regimen (> 10.6 mg/kg/d) may be excessive for some patients (increasing adverse effects but not efficacy);
- The optimal dose and treatment duration according to both initial viral load and HCV genotype.

Indications

These therapeutic schedules concern the following patient categories:
- Previously untreated patients who have no contraindication (i.e. the population in which these regimens were validated);
- Patients with HCV-HIV coinfection who were not previously treated for HCV infection (although they were not included in the two above-mentioned reference trials); particular attention must, however, be paid to the ribavirin interaction with some anti-HIV nucleoside analogs (d4T and ddI), which could favor mitochondrial cytopathy (risk of lactic acidosis) especially in patients with cirrhosis. A modification of antiretroviral treatment may be warranted;
- Patients who relapsed after IFN monotherapy (this type of situation should gradually become less frequent);
- Patients who did not respond to IFN monotherapy (although efficacy in this case needs to be evaluated).

1.2. Other therapeutic schedules

1.2.1. PEG IFN monotherapy

The recommended dose regimen is 180 µg/week of PEG IFN α-2a or 1 µg/kg/week of PEG IFN α-2b. The duration of treatment depends on the indication.

This treatment is indicated in the following situations:
- Patients with contraindications to ribavirin therapy, especially those with thalassemia; treatment should last 48 weeks if the aim is viral eradication;

- "Maintenance" treatment aimed at reducing the progression of fibrosis after prior virological failure; the duration of “maintenance” treatment will depend on biochemical response and tolerability; this regimen must be validated in clinical trials.

1.2.2. Standard IFN monotherapy

This treatment applies to two distinct populations: patients with acute HCV infection, and patients on dialysis.

1.2.2.1. Acute HCV infection

The only available studies were done with IFN monotherapy, and gave a rate of prolonged virological response exceeding 80% in recently published series. The jury recommends the use of one of the two schedules described in the literature that offer the best virological results (off-licence indication in France):

- IFN 5 MU/d for 4 weeks, then 5 MU three times a week for 20 weeks;
- IFN 10 MU/d until normalization of transaminase levels (observed after 3 to 6 weeks in the only relevant study).

Other therapeutic schedules, especially those using PEG IFN, with or without ribavirin, must be assessed in clinical trials.

Indications

- Asymptomatic acute HCV infection: if the infection has been documented (for example after accidental exposure to contaminated body fluids) by positivity for HCV RNA of at least two samples, some groups recommend starting treatment immediately. Others prefer to wait for an increase in transaminase levels before starting treatment. The jury could not advocate one or other of these approaches on the basis of current data;
- Acute icteric hepatitis C: the jury recommends not to treat immediately, as spontaneous recovery may occur in approximately 50% of cases. Detection of HCV RNA should be done 12 weeks after the onset of jaundice, and treatment should be started if the result is positive.

1.2.2.2. Dialysis

PEG IFN and ribavirin are currently contraindicated in dialysis patients. The proposed regimen consists of IFN 3 MU three times a week for 6 to 12 months. The injections are given after each dialysis session.

1.2.3. "Consensus" IFN

The place of this treatment remains to be specified. Its use is limited by the conditions of administration which are the same as those of standard IFN.

1.2.4. Ribavirin monotherapy

For patients with stage F3 fibrosis or cirrhosis in whom IFN is contraindicated or poorly tolerated, ribavirin monotherapy may be warranted, even though this strategy has not been sufficiently validated. This treatment should be maintained only in case of biochemical response.

1.2.5. Other combination treatments

There is no validated treatment regimen for patients who relapse or who do not respond to combination therapy. Combinations of PEG IFN with ribavirin, amantadine, mycophenolate are being assessed.

2. Liver transplantation

Hepatitis C accounts for about 20% of indications for liver transplantation in France. Liver transplantation is indicated for patients with "decompensated" cirrhosis and those with hepatocellular carcinoma (one tumor < 5 cm or 3 nodules < 3 cm each).

Graft reinfection is almost constant. The optimal antiviral treatment in this setting is currently under discussion. IFN monotherapy is not indicated. Combination therapy is being assessed.

3. Supportive measures

Certain factors influence the response to treatment and disease outcome. It is important to take these factors into account, as part of a overall patient management approach, whether or not treatment is indicated.

3.1. Alcohol consumption

Excessive alcohol consumption seems to be associated with an increase in viral replication and with resistance to antiviral treatment, and accelerates the progression of liver disease. Patients should thus be advised to abstain, or to drink less than 10 g/d.

Alcohol dependence must be treated. Antiviral treatment can be offered as part of a overall management approach to the HCV-infected alcoholic patient. Even in the absence of antiviral treatment, management of alcohol dependence is important to limit the progression of liver disease.

3.2. Obesity

Obesity is a risk factor for steatosis, which is associated with more rapid progression to fibrosis. It lowers treatment success rate. Weight reduction should be encouraged.

3.3. Smoking

One study suggests that smoking could increase the severity of liver disease. Considering the general health benefits of smoking cessation, the jury recommends that patients be advised to stop or to reduce their tobacco consumption.

3.4. Vaccination

Hepatitis B vaccination is recommended because HCV-HBV coinfection is associated with a poorer prognosis. The indications of hepatitis A vaccination are the same as in the general population.

3.5. Other treatments

No other treatments or dietary management have proven to be effective (including phlebotomy and ursodeoxycholic acid).

QUESTION 4. HOW TO MONITOR TREATED PATIENTS?

Patient monitoring during treatment must focus on efficacy and tolerability of treatment and on quality of life. In addition to regular visits to a specialist, proximity support is essential (ideally provided by a general practitioner), given the particularities of chronic HCV infection and its treatment. At least monthly visits to a general practitioner are required, and these should in no way be restricted to simple prescription of laboratory tests.

1. Assessment of treatment efficacy

In the absence of symptoms, efficacy is assessed on the basis of biochemical, virological and histological criteria.

1.1. Biochemical follow-up

In patients with initially high values, normalization or reduction of transaminase levels is a criterion of efficacy both during and after treatment. Transaminase levels should be measured every month during treatment and every two months for 6 months after treatment cessation. In patients in whom HCV has not been eradicated, transaminase levels should be measured once or twice a year.

1.2. Virological follow-up

Whatever the HCV genotype, the virological response (disappearance of detectable serum HCV RNA) must be assessed at the end of treatment and 6 months later by means of a sensitive qualitative technique (PCR or equivalent method). Sustained virological response is defined by undetectable HCV RNA 6 months after treatment cessation. This corresponds, in the vast majority of cases, to definitive viral eradication. A determination of serum HCV RNA can be performed 12 to 24 months after the end of treatment to detect rare cases of late relapse.

The prescription of tests to quantify HCV RNA depends on the viral genotype.

- In patients infected by **genotype 1**, decrease of viral load at 12 weeks is predictive of a sustained virological response. Treatment is adapted according to the results, as indicated in the answer to question 3. An alternative to HCV RNA quantitation is quantitative measure of HCV core antigen when viral load is high (current assay has a low sensitivity).
- Patients infected by **genotype 2 or 3** have a high probability of a sustained virological response. Viral RNA quantification at 12 weeks is not warranted. Virological response (disappearance of viral RNA) must be assessed at the end of treatment (24 weeks).
- In patients infected by **genotype 4, 5 or 6**, data are lacking and need to be obtained on the predictive value of HCV RNA measurement at 12 weeks. Qualitative HCV RNA assay could be performed 6 months after the beginning of treatment. When serum HCV RNA is still delected, treatment cessation should be discussed.

1.3. Histological follow-up

Liver biopsy is not required for patients with sustained virological response. In the absence of virological response, a new liver biopsy is only indicated if the histological result is likely to affect patient management. Non-invasive methods for assessing fibrosis may eventually replace liver biopsy but will first have to be validated.

2. Assessment of treatment tolerability

The adverse effects of antiviral drugs are dose dependent and often reversible. They can necessitate a dose reduction or premature withdrawal of the drug.

2.1. Adverse effects of interferon

♦ Some adverse effects, although compatible with treatment continuation, are frequent and can impact on quality of life. These include a 'flu-like' syndrome (fever, chills, headache, stiffness, etc.), fatigue, loss of appetite, weight loss, diarrhea, skin rash, hair loss, and inflammation at the injection site. The 'flu-like' syndrome can be prevented by paracetamol taken at the time of the injection (without exceeding 3 g/d). Dextropropoxyphene or ibuprofen (the latter only in the absence of cirrhosis) can be used if paracetamol is ineffective.

♦Psychiatric adverse effects are among the most severe. They range from irritability and mood changes to a severe depressive syndrome affecting one-third of patients. Continuation of treatment, in conjunction with antidepressant medication, should be discussed on a case-by-case basis after obtaining a specialist advice, according to the psychiatric manifestations, the severity of liver damage, and factors predictive of the response to antiviral treatment.

♦ Thyroid complications (hyper or hypothyroidism) are frequent, necessitating 3-monthly TSH testing (monthly in patients with pre-existing thyroid disorders).

♦ Hematological adverse effects (neutropenia and thrombocytopenia) can occur very early during treatment. They are more severe with PEG IFN than with standard IFN. The platelet count often stabilizes rapidly, but neutropenia can deteriorate throughout treatment. These adverse effects are more marked in patients with pre-existing neutropenia or thrombocytopenia (especially those with cirrhosis). They necessitate regular blood counts, twice during the first month then once a month throughout treatment. Further studies are necessary to evaluate the usefulness of hematopoietic growth factors in the treatment of these adverse effects.

♦Rarer complications include interstitial pneumonitis, retinal disorders, and skin disorders (pruritus, dry skin, aggravation of psoriasis).

♦IFNs are contraindicated in case of pregnancy.

2.2. Side effects of ribavirin

The main adverse effect of ribavirin is hemolytic anemia. This warrants regular hemogram (as during IFN therapy; see above). Dose may have to be decreased in the case of severe anemia. Further studies are required to evaluate the usefulness of erythropoietin in this indication.

Ribavirin can also cause nausea, dry skin, pruritus, cough and hyperuricemia. It is formally contraindicated in pregnant women because of its teratogenicity. Contraception for both partners is mandatory throughout treatment. Contraception must be continued for 4 months (women) and 7 months (men) after ribavirin cessation. Monthly β-HCG test and quarterly creatininemia and uricemia testing are recommended.

2.3. The special case of patients coinfected by HIV and HCV and treated with ddI or d4T

Clinical monitoring (body weight, lipodystrophy) and biological monitoring (hemogram, serum transaminase, lipase, creatine phosphokinase levels) must be reinforced in these patients. Any sign of mitochondrial cytopathy (risk of life-threatening lactic acidosis) calls for blood lactate measurement and, possibly, a modification of antiretroviral treatment. The risk appears to be increased by cirrhosis.

3. Quality of life during treatment

It is essential to inform the patient and friends/family of the impact of treatments for HCV infection on the quality of personal, family, social and professional life. Lifestyle advice must be given regularly (adequate fluid intake, physical activity, dietary advice, etc.). All professionals caring for these patients must keep a look out for psychiatric symptoms (especially suicidal ideas) and fatigue.

Mood changes and altered libido may necessitate discussion with the patient's family/friends. Medical networks and patient associations have an important role to play in supporting treated patients. Training should be reinforced in order to create and strengthen networks of general practitioners, hepato-gastroenterologists, nurses, psychologists, social workers, etc.

Training in self-injection is important to render patients more independent, although some will prefer a nurse to administer their treatment.

The jury recommends that all clinical trials in HCV infection include assessment of quality of life.

QUESTION 5. HOW TO MONITOR UNTREATED PATIENTS?

This question concerns patients for whom treatment was not indicated, and those who refused treatment. The overall aims are to provide support and to detect changes in the infection. It is important to provide these patients with regular information on the disease and its treatment, and lifestyle advice. A overall approach that takes comorbidity into account is required. General practitioners, proximity networks and patient associations can all make a contribution.

Monitoring modalities will depend on the stage of hepatitis at diagnosis, the patient's age, and changes in transaminase levels. Any increase in transaminase levels should be investigated in order to identify another potential cause (especially drug-related). Three different situations can be encountered:

- **The patient has no or mild lesions at liver biopsy**; the risk of progression is low but warrants monitoring, including half-yearly physical examination and transaminase measurement. A new liver biopsy is not recommended before 5 years unless transaminase levels increase or cofactors favoring progression of fibrosis are found;
- **Transaminase levels are persistently normal and liver biopsy has not been performed.** If transaminase levels remain normal, half-yearly physical examination and transaminase levels suffice. If transaminase levels increase, liver biopsy must be discussed especially if treatment is envisaged;
- **The patient has cirrhosis, with or without confirmation by liver biopsy.** Monitoring must be reinforced because of the risk of decompensation or hepatocellular carcinoma. No particular monitoring protocol has been validated, but the following approach can be recommended on the basis of usual practices:
    - alpha-fetoprotein measurement and abdominal sonography every 6 months, to detect hepatocellular carcinoma. Monitoring must be reinforced when the patient has factors predictive of progression to hepatocellular carcinoma (age over 50 years, male gender, chronic excessive alcohol intake, hepatocellular insufficiency, or increased alpha-fetoprotein);
    - upper GI endoscopy every 1 to 4 years, to detect esophageal or gastric varices.