Consensus conference report

French consensus conference on hepatitis C: screening and treatment

Foreword

This consensus conference followed the rules developed by the French *Agence Nationale pour le Développement de l'Evaluation Médicale (ANDEM)*. Briefly, this required an organising committee, a working group whose task was to make a comprehensive critical review of the literature before the conference was held, a panel of experts, and a jury. The conference was held over two days and included (*a*) a public session with presentations by experts working in areas relevant to the consensus questions, (*b*) questions and statements from conference attendees, and (*c*) deliberation by the jury, followed by the drafting of conclusions and recommendations.

Background

Hepatitis C virus (HCV), an enveloped RNA virus belonging to the *Flaviviridae* family, was identified in the late 1980s as the main causative agent of non-A, non-B hepatitis. The lack of effective culture has hindered assessment of diagnostic methods and treatments for HCV. Tropism is not restricted to hepatocytes, as HCV RNA sequences have been detected in peripheral blood mononuclear cells, among others.

HCV infection is characterised by a high risk of chronicity, and viral replication persists throughout the course of the disease. Hepatitis is a consistent feature of infection with HCV. Infection resolves spontaneously in about 20% of patients but persists in the remaining 80%. The estimated probability of cirrhosis is 20% after an average of 15 years. Once cirrhosis has developed, the patient is at risk of liver failure or hepatocellular carcinoma, or both; the yearly incidence of the latter is about 3–5%. HCV infection can also be associated with a variety of extrahepatic complications, some of which can be improved by antiviral treatment. The rate of progression to cirrhosis is influenced by several factors, especially age at the time of infection, sex and alcohol intake. Genetic factors linked to the HLA system and the viral genotype may also influence progression, although the role of these factors is controversial. The notable antigenic variability of the virus, which explains how it evades the immune response, complicates the development of an effective vaccine.

Strict selection of blood donors and the development of reliable serological tests have led to a considerable reduction in the risk of infection via transfusion. Intravenous drug use is currently the main risk factor for HCV infection in France. Other risk factors are less well documented, but nosocomial transmission has no doubt played a significant role. Among the 500 000 to 600 000 people infected in France, an estimated 80% are viraemic. Only a quarter of these seem to be aware that they have been infected.

The size of the infected population (despite the decreasing incidence) and the risk of severe complications within 10 to 30 years make HCV infection a serious public health problem. The authorities have launched awareness campaigns aimed at health care personnel and are encouraging the screening and management of patients through specific networks. Similarly, a very large number of clinical trials of antiviral agents, sometimes in combination with other therapeutic agents, have been completed or are ongoing. Some of these trials, generally sponsored by the pharmaceutical industry, have led to the approval of interferon α for the treatment of chronic hepatitis C. The complexity of the epidemiology of HCV, the paucity of research on this virus, the major economic and social implications of patient management, the possible long term severity of the disease, and uncertainties as to the efficacy of available treatment suggested an urgent need for a consensus conference, which was held on 16 and 17 January 1997 in Paris. The consensus jury was required to answer the following questions:

- Is screening for hepatitis C necessary?
- Is treatment for hepatitis C necessary?
- How should hepatitis C be treated?
- How should hepatitis C be monitored?
- What precautions should be taken to avoid transmission of HCV?

The conclusions and recommendations of the consensus conference were based on the most reliable data available at the time, taking into account the large number of outstanding questions and conflicting data on this rapidly evolving epidemic. A comprehensive review of the literature by the working group and the articles provided by experts have been published previously in French*. The conclusions and recommendations will need to be assessed in the light of new findings in a few years from now. This article aims to provide health professionals, particularly general practitioners, with a summary of current knowledge and with practical recommendations. Although the recommendations have been applied to a population in France, they are probably applicable to other countries with similar prevalences, such as the UK, Canada, and the USA.

Is screening for hepatitis C necessary?

Assessment of the value of screening for hepatitis C must include information on the prevalence of infection in both the general population and in specific high risk groups, the reliability of diagnostic assays, the natural history of infection, the benefits and risks of therapeutic intervention, and the potential benefits to society (benefits which may at times be conflicting). Moreover, the costs to society and the potential difficulties caused by the screening of individuals must be taken into account. Thus, the jury chose to examine the value of screening after defining the criteria which justify it.

CONDITIONS IN WHICH SCREENING IS JUSTIFIED

Screening is only warranted if the following conditions are met:

- The disease in question must be a public health problem because of its frequency or severity, or both. This is the

*A comprehensive review of the literature by the working group and the articles provided by experts have been published in French in a special issue of *Gastroentérologie Clinique et Biologique* (1997;**21**(1bis):S1–116).

case for hepatitis C, which affects an estimated 500 000 to 600 000 people in France and can lead to cirrhosis and hepatocellular carcinoma in the mid to long term.
- It must be possible to diagnose the disease by means of reliable, efficient tests that are acceptable to the subjects to be screened. This is the case for enzyme linked immunosorbent assays (ELISA) for antibodies to HCV.
- Screening must yield a clear benefit in terms of treatment or prevention, or both, at the individual or population level.
- Society must be prepared to pay the direct and indirect costs of screening. Potentially detrimental social and psychological consequences must be acceptable.

The third and fourth conditions generate the greatest problems. The costs and consequences of HCV screening have only been considered in preliminary studies.

RECOMMENDATIONS OF THE JURY

Mass screening, screening of targeted populations, and diagnosis of individual subjects must be considered separately.

Mass diagnosis

The cost effectiveness of mass screening for HCV is poor, as direct costs alone could reach several thousand million French Francs per country depending on the method used. Mass screening of the general population is not warranted. Targeted screening of risk groups should be considered and would yield similar results at a far lower cost.

Individual diagnosis

The value of individual diagnosis, sometimes at the patient's request, must be assessed by the physician concerned. HCV infection should be tested for in the case of an increase in aminotransferase activity. In these cases, the most appropriate diagnostic test is an ELISA for serum antibodies to HCV. These situations fall outside the scope of routine screening.

Targeted screening

Among the well documented risk factors, two stand out clearly: blood transfusion and intravenous drug use. Before the implementation of preventive measures, the risk of infection was about 6% per subject transfused. Blood transfusion is no longer an important risk factor as the residual risk is only about 1 in 200 000 donations. Intravenous drug use is currently the most important risk factor. Thus, the recommendations for these two populations are different.

Blood transfusion—Among patients transfused before 1991, the main aim is to identify those who are infected and can be treated. Medical personnel, particularly general practitioners, must make their patients more aware of this problem. Screening must be done pragmatically, with the intention of offering treatment to patients thus identified. A large number of these subjects qualify for treatment.

Practitioners' attention must be drawn to candidates for blood donation who are refused as donors during the medical interview preceding the donation. It seems logical to offer them an appointment at which HCV testing can be discussed.

Drug addiction—For current users of illicit injected drugs, the aim is ensure regular monitoring of high risk behaviour and prevent HCV infection via a comprehensive drug addiction management programme. The therapeutic aspect should not of course be neglected, especially as factors predictive of successful treatment are often present in these patients (young age, recent infection and non-type 1 genotypes). The use of disposable syringes seems to reduce the risk of HCV transmission. Screening efficiency may be lower for HCV than for HIV, suggesting that certain practices (sharing cotton wool, common use of materials other than syringes) increase the risk of HCV transmission. Similarly, a recent study suggested an increase in HCV transmission associated with "snorted" drugs (sharing of straws). Drug users are therefore an important target for regular HCV screening.

Former intravenous drug users should be screened in the same way as people transfused before 1991. The physician plays an essential role in the detection of this prior exposure.

Other risk groups—The prison population is at a high risk (strong prevalence of drug injection use, promiscuity, etc.) requiring a particular effort in prevention and screening.

Health care personnel, in whom the prevalence is similar to that of the general population, are not a risk group warranting regular routine screening. Nevertheless, screening may be wise for certain subgroups such as those working in dialysis units.

The nosocomial risk associated with certain medical and surgical procedures involving exposure to blood has decreased since the 1970s. In 1996, recommendations on the decontamination/disinfection of endoscopes and the sterilisation of biopsy forceps, which had been made several years previously by professional societies, were made compulsory. The jury considers it vital that these procedures are enforced and recommends that their application and efficacy are monitored. In the absence of precise information concerning the real risk of infection during invasive diagnostic and therapeutic procedures, the jury does not recommend routine screening. The jury does, however, recommend that epidemiological studies of this population be started rapidly.

Pregnant women are not at an increased risk of infection by HCV and infection does not influence either the course of pregnancy or the mode of delivery. The risk of transmission to the fetus is extremely low, unless the mother is also infected by HIV. There is currently no way of reducing the risk after conception. For these reasons, the jury does not recommend screening for HCV infection in pregnant women with no risk factors.

Screening for HCV among haemodialysed patients is already widespread. Nursing personnel in haemodialysis units are a high risk subgroup and should therefore be screened.

Screening of haemophiliacs began in 1991.

SCREENING METHODS

Scientific data and the initial cost effectiveness assessments clearly show that a single third generation ELISA adequately detects antibodies to HCV. The results of the test must be expressed as a ratio, and not in a purely qualitative manner. The sensitivity and specificity of available ELISAs make routine secondary testing unnecessary. However, if the result is positive, it is reasonable to test a second sample to rule out laboratory error. Routine confirmatory analytical tests (e.g. RIBA) are unnecessary when the ELISA is positive. Viral RNA should be measured in serum in the following circumstances: doubtful serological results, when the aminotransferase activity is repeatedly normal in an ELISA positive subject, and when there are other potential causes for high aminotransferase activities (heavy drinking, overweight, etc.). Standardisation, licensing of screening laboratories and quality control are necessary to ensure that testing for HCV RNA is as reliable as in reference laboratories. The value of tests for viral RNA in hepatocytes and mononuclear cells as a predictor of long term response is being assessed. Regional and/or national action to standardise aminotransferase

assays, similar to those in force in transfusion centres, should be undertaken as soon as possible.

Is treatment for hepatitis C necessary?

Treatment of hepatitis C aims to improve the natural progression of the disease, which is dominated by the risk of cirrhosis and hepatocellular carcinoma. This treatment must have few, "acceptable" side effects, as the great majority of subjects are asymptomatic. Eradication of the virus can be another theoretical aim of treatment. It is not currently known whether the disappearance of the virus from serum is sufficient to prevent severe hepatic lesions. Furthermore, the presence of the virus is not always associated with the onset of severe lesions.

Results of clinical trials are difficult to analyse for two reasons: firstly, the lack of standard end points for efficacy (those used are biological (alanine aminotransferase, ALT), virological (serum HCV RNA) and histological (activity and fibrosis scores)) and secondly the short follow up periods relative to the long natural history of hepatitis C.

DRUGS

Interferon α, currently the only effective drug, has been approved in France for the treatment of chronic hepatitis C. Other drugs such as ribavirin are undergoing efficacy trials.

INDICATIONS

The indications for treatment will be discussed in four different situations: (1) chronic active hepatitis, (2) cirrhosis, (3) acute hepatitis, and (4) possible recent infection with no signs of acute hepatitis.

The indications for treatment of extrahepatic manifestations of HCV infection were not dealt with at this consensus conference.

Chronic hepatitis

Chronic hepatitis is now described as mild, moderate and severe rather than chronic active hepatitis. Treatment is recommended given the possibility of progression to cirrhosis and hepatocellular carcinoma. Treatment modalities should only be considered after a thorough work up based on an interview, biological tests and histological evaluation of the liver.

The following points should be focused on during the interview: (1) characteristics of the infection (date and route), (2) extrahepatic manifestations (cryoglobulinaemia, etc.), (3) factors capable of influencing the therapeutic decision, such as ongoing excessive alcohol consumption or drug addiction, depression or a history of depression, and autoimmune thyroiditis. Box 1 summarises the biological tests for HCV.

Currently it seems logical to measure viraemia before starting antiviral treatment. For practical reasons, the jury recommends routine testing using the polymerase chain reaction (PCR) if treatment is indicated. In the future, a standardised, sensitive, quantitative assay for HCV viraemia would be preferable to the current PCR method. The jury recommends that these tests be supplemented by HCV genotype determination. Together with viral load, this is the main predictive factor of response to interferon α. These two factors are also useful in terms of the information given to the patient.

Histological study of the liver is crucial. It has two aims: firstly, to assess lesions, with separate quantification of necroinflammatory activity and fibrosis, using the METAVIR system (table 1), which should now be used in preference to the Knodell score; and secondly to identify associated disease conditions potentially contributing to the onset or aggravation of fibrosis, including alcoholic lesions, lesions due to a viral co-infection (HBV, HDV, HIV), and late cutaneous porphyria. Needle biopsy of the liver must be carried out by a trained clinician, preferably with ultrasound guidance.

Box 1 Pretreatment biological tests

- Alanine aminotransferase
- Antibodies to HCV
- Viral RNA in serum by polymerase chain reaction
- Hepatitis B surface antigen
- HIV serology (plus the CD4 lymphocyte count if positive)
- Full blood cell count, including platelets
- γ-glutamyltranspeptidase
- Alkaline phosphatase
- Bilirubinaemia
- Albuminaemia
- Prothrombin time
- α-fetoprotein
- Glycaemia
- Creatininaemia, proteinuria
- Serum iron, transferrin saturation coefficient, ferritinaemia
- Anti-smooth muscle antibodies
- Anti-nuclear antibodies
- Anti-LKM-1 antibodies
- Anti-mitochondrial antibodies
- Thyroid stimulating hormone
- Anti-thyroperoxidase antibodies
- β-human chorionic gonadotropin (in women of childbearing potential not using effective contraception)
- Cryoglobulinaemia (if the clinical context is relevant)

Formal contraindications to treatment with interferon α should be identified before treatment (box 2)

The therapeutic decision—In the absence of contraindications to interferon α, the jury agreed that *subjects with chronic active hepatitis (METAVIR score > A2)* should be treated. Patients who consume more than 20 g of alcohol daily should be effectively weaned before starting treatment. Likewise, an attempt should be made to wean drug addicts durably and completely before starting treatment, possibly with the assistance of replacement products. Over 65 years, age itself is not a contraindication to treatment, and the decision to treat should thus be made on an individual basis.

Table 1 METAVIR score

	*Lobular necrosis**		
	Absent 0	*Moderate 1*	*Severe 2*
Score A (activity)			
Piecemeal necrosis†			
Absent 0	A0	A1	A2
Minimal 1	A1	A1	A2
Moderate 2	A2	A2	A3
Severe 3	A3	A3	A3
Score F (fibrosis)			
No portal fibrosis	F0		
Stellar portal fibrosis with septae	F1		
Portal fibrosis with rare septae	F2		
Numerous septae with cirrhosis	F3		
Cirrhosis	F4		

*Lobular necrosis (LN): intralobular necroinflammatory focus (foci). 0, less than one LN per lobule; 1, at least one LN per lobule; 2, several LN per lobule or confluent necrosis or bridging necrosis.
†Piecemeal necrosis (PN). 0, no PN; focal PN in contact with a few portal spaces; 2, diffuse PN in contact with a few portal spaces or focal PN in contact with all portal spaces; 3, diffuse PN in contact with all portal spaces.

Box 2 Formal contraindications to treatment with interferon α
- Pregnancy
- Severe endogenous depression
- Severe renal failure
- Severe cytopenia
- HIV infection with lymphocyte depletion
- Autoimmune hepatitis
- Autoimmune thyroiditis (especially in cases of hyperthyroidism)
- Severe heart disease
- Epilepsy poorly controlled by treatment

The decision to treat should always take into account the patient's motivation. The patient should be informed of the expected benefits of treatment and its possible adverse effects.

The jury recommends that patients with repeatedly normal ALT or minimal hepatic lesions, or both, should only be treated in clinical trials.

The following special cases were envisaged:
- Kidney transplantation: treatment with interferon α is contraindicated because of the frequency of severe kidney damage (irreversible renal failure) and the risk of rejection.
- Heart transplantation: treatment with interferon α is contraindicated because of the risk of rejection.
- Liver transplantation: treatment with interferon α alone is contraindicated because it is poorly effective and carries a risk of rejection.
- HIV infection: the decision to treat with interferon α will depend on the patient's immune status. Treatment can only be envisaged in HIV infected subjects without major lymphocyte depletion.
- Cirrhosis: at this stage, the impact of treatment with interferon α on survival and/or the prevention of complications of cirrhosis (especially hepatocellular carcinoma) has yet to be determined. The jury thus recommends that patients at this stage of disease should not be treated. This attitude may be different in case of notable biological or histological, or both, activity. The results of ongoing clinical trials may modify this opinion.
- Acute hepatitis: the diagnosis of acute hepatitis C is based on an increase in serum ALT activity and positive viraemia within six months of HCV infection. Interferon α, 3 MU three times a week for at least three months, reduces the risk of progression to chronicity and is therefore recommended.
- Accidental exposure to HCV infected blood: given the lack of a universally approved approach, the jury proposes the following guidelines: immediate local washing, immediate sampling of the potentially infective person and the exposed subject to test for anti-HCV antibodies and HCV RNA, notification of the accident, and estimation of the risk (depth of the wound, type of needle, clinical and virological status of the infected subject). It seems logical to assay ALT activity every two weeks for two months and then every month for four months, to perform PCR after two months, and to test for anti-HCV antibodies at three and six months. If acute hepatitis develops, treatment with interferon α for at least three months is recommended.

How should hepatitis C be treated?

In France, the only drug approved for the treatment of chronic hepatitis C is interferon α. Other treatments are being assessed in combination with interferon α (ribavirin, an antiviral agent, and other non-antiviral drugs).

INTERFERON α ALONE

Acute hepatitis

Acute hepatitis C is rarely detected by the patient or physician because it is frequently asymptomatic. A meta-analysis of four randomised trials involving a total of 134 patients with acute post-transfusional hepatitis showed the efficacy of treatment with interferon α at a dose of 3 MU three times a week for three months. The jury endorses this treatment and recommends a further three month course of the same drug if viral RNA persists after three months of treatment.

Chronic hepatitis

At present, chronic active hepatitis is the only form of chronic hepatitis for which treatment is recommended. Treatment is based on interferon α, which has been tested in several clinical trials. The jury stresses several important points about these trials: (1) the treatment schedules were extremely varied; (2) the duration of post-therapeutic follow up was always short relative to the natural history of the disease; (3) end points for efficacy differed; and (4) the extrapolation of results by the experts involved is controversial.

It is generally agreed that interferon α 3 MU three times a week for 12 months offers the best results in terms of efficacy and tolerableness. The jury regards this protocol as the reference treatment for chronic active hepatitis C.

Based on their response to treatment, patients can be divided into three subgroups: responders, non-responders and those who relapse.

Responders—An initial response is normalisation of ALT activity during treatment. This generally occurs rapidly and is observed in approximately half the patients at the end of treatment.

Sustained responses are characterised by persistent normalisation of ALT activity more than six months after treatment withdrawal. This is generally accompanied by the disappearance of viral RNA from serum, which occurs in about 80% of cases. A sustained response is observed in roughly one third of patients (10–45%). This wide range of values may reflect the heterogeneity of the populations treated. Sustained responses are also accompanied by a reduction in histological activity. These results are supported by a recent meta-analysis that showed the benefit of 12 months of treatment in terms of durable normalisation of ALT activity and histological improvement, relative to untreated patients and patients who received a shorter course of treatment.

The main factors predicting a good response to treatment are the following: female sex, young age, absence of even moderate alcohol consumption, absence of iron overload, cholestasis and obesity, a viral genotype other than type 1, and a low viral load. These predictive factors have not been evaluated prospectively in a sufficient number of studies to allow them to be taken into account in the decision to treat. Conflicting results among the different studies may be linked to heterogeneous distribution of these factors in the populations studied.

Some studies suggest that treatment for more than 12 months leads to a higher frequency of sustained responses, but this needs to be confirmed. The use of higher doses of interferon α in this setting leads to the more frequent occurrence of side effects.

Recent studies suggest that disease progression is stopped for several years when response persists six to 12 months after treatment withdrawal. It remains to be seen whether this treatment prevents late complications (cirrhosis and especially hepatocellular carcinoma). The jury

recommends large, long term cohort studies and the creation of registers on hospital–community networks.

Patients who relapse—Relapse is characterised by normalisation of ALT activity during treatment, followed by a new increase after treatment withdrawal. This occurs in nearly half the patients who have a good initial response, generally within six months of treatment withdrawal. There is a relatively good correlation between a re-increase in ALT activity and the reappearance of viral RNA in patients who relapse, although these two variables may not be associated.

A second 12 month course of interferon α is effective in patients who relapse after an initial six month treatment period. This has not been observed in the case of relapses occurring after an initial 12 month treatment period.

Non-responders—The absence of response is characterised by the failure to normalise ALT activity during treatment and the persistence of viral RNA in serum. No notable histological improvement has been observed in non-responders some time after treatment.

When aminotransferases fail to normalise three months after the beginning of treatment, a later response is highly unlikely. In such cases, there is no evidence that further treatment with interferon α, or a dose increment, is effective. Consequently, the jury considers that interferon α can be stopped after three months of treatment if no response is obtained.

COMBINATION THERAPY WITH INTERFERON α

The association of interferon α with ribavirin seems to be the only promising drug combination currently available. There have been few trials and few validated publications. Existing trials involved previously untreated patients, patients who had relapsed, and non-responders. Tolerability was satisfactory. Efficacy seems to be good in patients who relapse. The combination seems to be far less beneficial in non-responders. Pending the results of larger trials, the jury does not recommend the use of ribavirin in combination with interferon α.

Other drug combinations are being tested, but none has been sufficiently documented. In addition, the results of these studies are conflicting. This rules out the use of these combinations in routine practice. Two combinations warrant further study: preliminary therapeutic bleeding before treatment with interferon α in patients with iron overload, and administration of ursodeoxycholic acid to patients with cholestasis.

How should hepatitis C be monitored?

MONITORING OF UNTREATED CHRONIC HEPATITIS C

This concerns patients for whom treatment is not indicated and those who refuse treatment.

three clinical situations can be distinguished:

- The patient has no cirrhosis (or notable fibrosis) and was infected about 20 years previously. The risk of progression is considered negligible. No particular monitoring is required.
- The patient has no cirrhosis (or notable fibrosis) but was infected more recently. The risk of progression warrants monitoring, which will comprise a yearly physical examination, liver tests and possibly abdominal ultrasonography. A new liver biopsy is recommended after three to five years to assess liver damage. Regular alcohol intake calls for closer monitoring. Its additive effect together with HCV on histological lesions of the liver contributes to the risk of cirrhosis (relative risk multiplied by a factor of 7 to 9).
- The patient has cirrhosis. Monitoring should be reinforced to detect progression of cirrhosis, especially towards hepatocellular carcinoma. Factors identified as being predictive of hepatocellular carcinoma in most studies are: age, male sex, alcohol consumption, the degree of hepatocellular failure, a moderate increase (persistent or fluctuating) in α-fetoprotein, and the presence of small cell or large cell dysplasia on liver biopsy (if available). No particular monitoring schedule has been validated. The jury makes the following recommendations based on clinical practice:
  (a) every six months: liver tests, α-fetoprotein assay and abdominal ultrasonography; and
  (b) every one to four years: upper gastrointestinal endoscopy to detect oesophageal or gastric varices. Closer monitoring is required for patients with factors predictive of progression to hepatocellular carcinoma.

MONITORING OF TREATED CHRONIC HEPATITIS C

Monitoring of patients treated with interferon α for hepatitis C includes the assessment of therapeutic efficacy and side effects.

Assessment of efficacy

In the absence of clinical manifestations, monitoring of efficacy is based on biological, virological and histological criteria.

- ALT activity is the main criterion of efficacy during and after treatment. It should be assayed every month during treatment, then at the intervals indicated in table 2. Other biological parameters such as γ-glutamyltranspeptidase, bilirubinaemia, prothrombin time, and albuminaemia have sometimes been proposed, but their value is controversial. The value of biological markers of fibrosis has not been confirmed yet.
- Serum should be tested for the presence of viral RNA at the third month of treatment, at the end of treatment and six months later (table 2). A negative PCR result indicates remission of HCV infection. During treatment, a normal ALT activity but persistence of viral RNA suggests that relapse is likely when interferon α is withdrawn. The value of tests for viral RNA in hepatocytes and mononuclear cells as predictors of long term response is being assessed.
- Liver biopsy can be indicated at various times according to response to treatment. Routine biopsy has little value for monitoring short term treatment. In non-responders, including those with normal ALT activity

Table 2 Proposed routine monitoring of the efficacy and tolerableness of treatment with interferon α in patients with chronic hepatitis C

	Treatment (month)												*Post-treatment follow up (month)*				
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*14*	*16*	*18*	*21*	*24*
Efficacy																	
Clinical	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ALT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HCV RNA			X									X			X		
Tolerableness																	
WBC and platelet count	X	X	X	X	X	X	X	X	X	X	X	X					
TSH			X			X			X			X			X		

WBC, white blood cell; TSH, thyroid stimulating hormone.

but a positive PCR result, it seems reasonable to perform a biopsy after three to five years.

Side effects of treatment
Side effects result in discontinuation of treatment in roughly 15% of patients. They are dose dependent and rarely severe.

Side effects of a psychiatric nature are the most severe. Depression occurred in 7% of treated patients and led to suicide in 0.2% of cases. Delirium, confusion and seizures are even less common.

Thyroid complications (hypo- or hyperthyroidism) are relatively frequent and generally occur in the first few months of treatment. Hyperthyroidism necessitates withdrawal of treatment, although not all thyroid complications resolve after treatment withdrawal. The presence of antibodies to thyroperoxidase before treatment is predictive of thyroid disorders.

Cardiovascular complications (particularly arrhythmias) only occur at doses of interferon α higher than those currently recommended.

Mild and moderate side effects are frequent. A flu-like syndrome occurs shortly after the beginning of treatment in half the patients receiving 3 MU per injection. Fatigue can persist throughout the treatment period. Reversible hair loss is reported in 16% of patients treated. Neutropenia or moderate thrombocytopenia, or both, are frequent during treatment but rarely have clinical consequences.

The frequency and occasional severity of side effects linked to interferon α necessitate regular biological and clinical monitoring (table 2). Glycaemia should be checked regularly in diabetic subjects. The intervals and type of investigations can vary according to the clinical context.

What precautions should be taken to avoid transmission of HCV?

The diagnosis of HCV infection requires specific precautions on the part of medical personnel and the patient, both for himself (or herself) and those with whom he (or she) is in contact.

PRECAUTIONS TO BE TAKEN BY MEDICAL PERSONNEL

Universal hygiene rules must be applied to all medical procedures in community offices, at the patient's home and in the hospital. Regulations aimed at protecting patients undergoing diagnostic and therapeutic procedures must be strictly applied; all medical personnel are individually responsible for applying these recommendations.

Transfusion
The Direction Générale de la Santé/Direction des Hôpitaux (DGS/DH) circular No. 609 dated 1 October 1996 and based on the decree of 24 January 1994, regarding haemovigilance rules, requires that a document stating the circumstances in which transfusions are given be sent to each patient. It also recommends serological follow up for HCV and ALT activity, particularly three months after the transfusion. Haemovigilance regulations also make a number of demands on health care personnel, particularly to ensure that transfused products are traceable. Traceability is based on returning a nominative distribution file to the blood transfusion centre to check which patients received which products.

The diagnosis of HCV infection in a blood donor means that any donations must be destroyed, that HCV seropositivity must be confirmed by a new ELISA test, and that the donor must be informed. HCV infection formally contraindicates blood donation.

The discovery of HCV seropositivity in a regular blood donor calls for an investigation to identify recipients, with a view to their screening and management.

Organ and tissue donation
HCV can be transmitted via infected donor organs and tissues (100% risk in case of viral replication in the donor). All HCV infected subjects must therefore be excluded from the list of potential donors.

Medical procedures
Given the lack of an effective culture system for HCV, it has not been possible to assess the sensitivity of the virus to the different disinfectants and cleansing agents. The efficacy of a disinfection method is currently based on the detection by PCR of viral RNA in instrument rinsing fluids.

Certain procedures have been incriminated in the nosocomial transmission of HCV. They include haemodialysis, vascular catheterisation, dental care, peri-anesthetic procedures, and gastrointestinal endoscopy.

The most effective means of reducing HCV transmission is strict compliance with universal precautions, based on hand washing and decontamination, cleaning, disinfection and sterilisation of the materials used, without forgetting to decontaminate worktops, furniture and mobile equipment.

Decontamination/disinfection of endoscopes is effective if current rules are respected (DGS/DH circular No. 236; 2 April 1996)—that is, use of totally immersible equipment, sterilisation of biopsy forceps, decontamination of the device, and disinfection in 2% glutaraldehyde for 20 minutes.

Accidental exposure to blood and other body fluids
The information leaflet (DGS/DH No. 666) dated 28 October 1996 lists the measures to be taken in case of accidental exposure to blood and body fluids—that is, cleansing in soapy water, rinsing, and prolonged antisepsis (at least 10 minutes) in Dakin or 12% bleach diluted 1 in 10. In the case of mucosal exposure immediate, lengthy rinsing with water or normal saline, assessment of the risk by a specialist, serological testing of the affected person and the source patient, and notification of the accident. Basic precautionary measures should also be used, such as not recapping needles, use of puncture proof containers, and wearing protective glasses when there is a risk of aerosol transmission.

Infected drug addicts
The prevention of HCV transmission by infected drug users is based on the same measures as for HIV—that is, free supply of syringes, availability of complete single-use injection kits, replacement treatment, and distributors combined with disposal bins. Given the early nature of HCV infection during illicit drug use, subjects at risk must be warned that the first shared syringe can be infective. Clean straws should be used for snorting drugs.

PRECAUTIONS FOR HOUSEHOLD AND SOCIAL CONTACTS

Sexual intercourse
The risk of HCV transmission by the sexual route seems to be very low in the absence of identified risk factors—that is, traumatic intercourse or intercourse during the menstrual period, and preexisting genital lesions (usually associated with sexually transmitted diseases).

Persons infected by HCV should be given the following advice:

- the risk of HCV transmission during sexual intercourse is very low, but cannot be totally excluded;
- patients with only one sexual partner should abstain from intercourse, or use condoms, during the menstrual period or in the case of genital lesions;

- the partner should be advised to have a test for HCV infection, and be informed of the very low risk of positivity in the absence of other risk factors, and the fact that regular testing is not necessary;
- in case of multiple sexual partners, condoms should be used to minimise the risk of contracting not only HCV but also other viruses.

Family

The following advice can be given:

- avoid potential blood–blood contact by not sharing toiletry objects such as razors, toothbrushes, dental descaling materials, nail clippers, and hair removal devices.
- cuts and skin wounds should be dressed immediately after cleansing and disinfection;
- common objects such as cutlery, drinking glasses, etc., do not require disinfection;
- greeting kisses do not transmit HCV;
- family members do not need to be tested for HCV, apart from the sexual partner, children potentially infected at birth, and those with a personal risk of parenteral infection, whether or not it is shared with the infected person. This risk can be evaluated during individual interviews with each member of the family, when information on risks of transmission can also be given.

Social contacts

As HCV transmission is essentially parenteral, social relations do not carry any particular risk of infection. There is no reason to isolate socially people infected by HCV; this applies particularly to HCV infected children attending school or kindergarden. Sports are permitted. As with HBV and HIV, cuts and other skin lesions must be dressed immediately after disinfection.

Mother–child transmission

HCV infected women who wish to have children or are already pregnant should be given the following advice:

- in the absence of detectable HCV RNA in the mother, the risk of transmission to the child is virtually nil;
- pregnancy is not contraindicated, even in case of viral replication. The risk of transmission is low, except in case of high viral load and/or co-infection by HIV;
- vaginal delivery is not contraindicated.
- breastfeeding is not advisable;
- the infant should be tested for the presence of HCV RNA six months or a year after birth. Antibodies to HCV can only be detected for after the age of one year.

PRECAUTIONS FOR PERSONS INFECTED BY HCV

- There are currently no scientific data warranting a particular diet. However, in the case of notable excess weight, weight loss is recommended to improve the assessment and, possibly, the efficacy of treatment with interferon α.
- Regular, even moderate alcohol consumption should be avoided. Alcohol and HCV have an additive effect for the risk of cirrhosis. Alcohol increases viral replication, promotes viral mutations, and increases the severity of histological lesions of the liver.
- Vaccination against hepatitis B is recommended.
- Except in rare circumstances, HCV infection does not involve any particular constraints in the workplace.

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