Hepatitis C : Screening, treatment and prevention Practical guidelines

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Introduction

Hepatitis C is a major health problem worldwide. According to the WHO, there are an estimated 170 million people infected with hepatitis C virus (HCV) (1). In Belgium, the prevalence of hepatitis C is approximately 1% (2). Blood transfusion used to be a major risk factor for acquiring HCV infection before screening for antibodies to HCV in the early nineties (in Belgium : from 01.07.1990 on). Injection drug use is now the most frequently identified risk factor for acquiring this infection. Thirty seven to 98 % of the intravenous drug users are seropositive for HCV (3,4).

Approximately 80% of HCV infected patients develop chronic hepatitis C. About 20% of these patients will develop severe chronic hepatitis C and cirrhosis, which becomes detectable in the second and third decade after infection. In the presence of cirrhosis, there is a 1-4% yearly risk of developing hepatocellular carcinoma (5). Because chronic liver disease may develop many years after acute hepatitis C virus infection, the past incidence of acute infection is a major determinant of the future burden of HCV associated complications. Although the prevalence of HCV infection may be declining because of the decline in incidence in the 90s, the number of persons infected for ≥ 20 years could increase substantially before peaking in 2015 (6).

In most infected people the infection remains unrecognised, and most of those with a diagnosed infection have not been treated (7). Up to recently, the treatment for chronic hepatitis C was relatively ineffective and fraught with side effects. Therefore many physicians were reluctant to offer therapy to their patients. During the last years, however, the knowledge of hepatitis C has increased dramatically, and more effective therapies became available, leading to the need to re-examine the approaches to management and treatment. In 2002, two consensus conferences on hepatitis C were hold : one in France (8) and one in the USA (9). At this moment, when the new pegylated interferons become available in Belgium, the Steering Committee of the BASL estimates that guidelines should be given in matters of screening, treatment and prevention of hepatitis C. These recommendations should be of use for medical specialists, general practitioners and patients.

1. Screening

Patients at risk for hepatitis C infection are those exposed to risk factors. Major risk factors are blood transfusion before 01.07.1990, date of start anti-HCV testing (with first generation tests) on blood and blood derivatives in Belgium, and intravenous drug abuse. Minor risk factors are sexual, mother-to-infant transmission, household contact or nosocomial contamination (10). Transmission of hepatitis C virus due to invasive medical procedures is possible but rare. The risk of digestive endoscopy seems much lower than for other procedures such as urological procedures in the Belgian experience (11) or ocular surgery in the Italian experience (12). Mass screening for hepatitis C is very expensive and therefore not cost-effective (13).

1.1. *Persons to be screened*

Screening for hepatitis C is appropriate in the following risk groups :

- Persons who had following medical events in Belgium before 01.07.1990, starting date of anti-HCV testing of blood and blood derivatives :

– blood transfusion
– major surgical procedures (cardiac, vascular, digestive, pulmonary, gynaeco-obstetric, orthopaedic, …)
– stay in intensive care unit including neonatal intensive care
– difficult parturition
– digestive bleeding
– tissue, cell or organ transplantation

- Dialysis patients
- Persons who were drugs users by intravenous or intranasal route
- Children from mothers seropositive for HCV

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- Sexual partners and household members of patients with HCV
- Persons who had tattoos, piercing, acupuncture without use of single use or personal equipment
- Persons who had medical care in countries with high prevalence of HCV (South East Asia, Middle East, Africa, South America)
- Persons with unexplained elevations of transaminases
- Patients seropositive for HIV or HBV
- Persons with unexplained asthenia
- Persons with history of unexplained jaundice

1.2. *Screening tests*

Screening is performed by 3rd generation ELISA tests. These tests have an accuracy of more than 99%, rendering confirmation by RIBA unnecessary. A negative ELISA test excludes hepatitis C in a large majority of patients.

2. Follow up of patients with anti-HCV

- When anti-HCV is present, ALT level should be determined. A single determination of ALT level gives limited information about the severity of the underlying liver disease. Patients who initially have a normal ALT should undergo 3 measurements over a six months period to confirm persistence of normal ALT levels.
- When anti-HCV is present and ALT is normal, qualitative HCV RNA determination should be performed (sensitivity of 50 IU/mL) in order to confirm HCV infection. When HCV RNA is negative, the presence of anti-HCV is probably due to past infection. When HCV RNA is positive, annual follow-up is proposed, but no treatment is considered. A liver biopsy is not indicated.

When anti-HCV is present and ALT is elevated, even slightly, a qualitative HCV RNA determination is indicated in order to confirm the presence of HCV.

- A quantitative HCV RNA determination (which is less sensitive than the qualitative) and genotyping is only indicated when treatment is considered.
- Liver biopsy is not recommended in patients with normal transaminases. In contrast, a liver biopsy is highly recommended before considering treatment in order to determine the inflammatory activity and the degree of fibrosis (staging), and to exclude other liver diseases. When it is decided not to treat, a follow-up biopsy is planned after 3 to 5 years in order to determine the evolution of the disease.

3. Treatment

3.1. *Results of recent trials in patients with chronic hepatitis C*

Currently the best indicator of effective treatment is a sustained virologic response (SVR). This is defined by the absence of detectable HCV RNA in the serum as shown by a qualitative HCV RNA assay with a lower limit of detection of 50 IU/mL or less at 24 weeks after the end of treatment.

Three large pivotal trials have shown the superiority of pegylated interferon plus ribavirin over standard interferon-ribavirin combination, especially in genotype 1 (14-16).

The study of Manns et al. (14) included 1530 patients randomized in 3 groups treated for 48 weeks : pegylated interferon alpha-2b 1.5 µg/kg qw and ribavirin 800 mg qd ; pegylated interferon alpha-2b 1.5 µg/kg qw for 4 weeks, then 0.5 µg/kg qw for 44 weeks and ribavirin 1000-1200 mg qd, or standard interferon alpha-2b 3 MU tiw and ribavirin 1000-1200 mg qd. The SVR was higher in the pegylated interferon alpha-2b 1.5 µg group (54%) than in the standard group (47%) ($p = 0.01$). In genotype 1, SVR was 42% versus 33% in the pegylated interferon 1.5 µg group and standard treatment group ($p = 0.02$) respectively. In genotype 2 or 3, SVR was 82% versus 79% (not significant). In this trial a ribavirin dose of 800 mg was selected in combination with the higher peginterferon alpha-2b dose because of concern of anaemia, what in fact did not occur. A retrospective analysis showed that adherent patients, i.e. those who received at least 80% of the total interferon dose with at least 80% ribavirin dose for at least 80% of the expected duration of therapy, had a SVR rate of 63%. Those treated with ≥ 10.6 mg/kg/d ribavirin had a SVR of 72%. In patients with genotype 1 these figures were 51 and 63% respectively in adherent patients and those adherent who received ≥ 10.6 mg/kg/d ribavirin (16).

The study of Fried et al. (15) included 1121 patients randomised in 3 groups treated for 48 weeks : pegylated interferon alpha-2a 180 µg qw and ribavirin 1000-1200 mg qd, or pegylated interferon alpha-2a and placebo, or standard interferon alpha-2b 3 MU tiw and ribavirin 1000-1200 mg qd. The SVR were 56%, 29% and 44% respectively ($p = 0.001$, for peginterferon alpha-2a plus ribavirin versus interferon alpha-2b plus ribavirin). In patients with genotype 1, SVR were 46, 21 and 36% respectively ($p = 0.01$ for peginterferon alpha-2a plus ribavirin versus interferon alpha-2b plus ribavirin). In patients with genotypes 2 and 3, the SVR were 76%, 45% and 61% respectively ($p = 0.005$ for peginterferon alpha-2a plus ribavirin versus interferon alpha-2b plus ribavirin).

A recent multicentric study of peginterferon alpha-2a and ribavirin was only published in abstract form (17). Using a stratification based on genotype and initial viral load, 1,284 patients were treated with a constant dose of peginterferon alpha-2a (180 µg qw) but randomised in 4 regimens according to the duration of therapy (24 versus 48 weeks) and dose of ribavirin (800 versus 1000-1200 mg qd). In patients infected with genotype 1, the highest rates of response (51%) were achieved in patients treated for 48 weeks with the higher dose of ribavirin. In patients with genotypes 2 and 3, SVR ranged from 73 to

78%, regardless of duration of therapy or ribavirin dose. This indicates that these patients are adequately treated with a 24 week course of peginterferon alpha-2a and that the dose of ribavirin can be reduced to 800 mg qd in this group.

The data concerning the 49 patients infected with genotype 4 in the two studies with peginterferon alpha-2a plus ribavirin (15,17) were recently analysed (18). The optimal regimen in this patient population was peginterferon alpha-2a plus ribavirin 1000-1200 mg qd for 48 weeks. A 79% SVR rate was obtained, similar to the response rate in genotypes 2 and 3, provided that the patients were treated exactly as those infected with genotype 1.

The number of patients with other genotypes was too small in these trials to draw firm conclusions.

In all these studies, factors associated with successful therapy included genotype 2 and 3, lower baseline viral levels, less fibrosis on liver biopsy and lower body weight or body surface area.

Based on the results of bove mentioned studies (14,15) and on recent consensus statements (8,9), Peginterferon + ribavirin is now considered as the reference therapy for all chronic hepatitis C patients.

3.2. *Which patients should be offered treatment ?*

All patients with chronic hepatitis C, in whom HCV RNA is detected (> 50 IU/mL) are potential candidates for treatment. Patients eligible for treatment are in any case those patients with one or more of the following conditions :

– elevated ALT levels
– liver biopsy with portal or bridging fibrosis and at least moderate inflammation and necrosis
– extrahepatic manifestations (especially vasculitis)

In other conditions (mild chronic hepatitis C, normal transaminases), risks and benefits of therapy are less clear and should be determined on individual basis or in the context of clinical trials. Simple monitoring without treatment is recommended.

Treatment may, however, also be considered for patients who are highly motivated and do not fulfil these criteria, especially when the genotype is 2 or 3, such as young women willing to avoid any risk of vertical transmission.

Patients candidate for treatment may be naïve, patients, who were never treated or relapsers to interferon monotherapy. Other cases such as nonresponders to interferon monotherapy or relapsers to interferon-ribavirin combination treatment should be treated in clinical trials as the efficacy of peginterferon + ribavirin remains to be validated.

3.3. *Recommended regimens*

- Peginterferon alpha-2b based

Peginterferon alpha-2b 1.5 µg/kg/wk + ribavirin (800 mg qd if < 65 kg ; 1000 mg qd if 65-85 kg ; 1200 mg qd if > 85 kg), during 48 wk for genotypes 1, 4, and 24 weeks for genotypes 2 and 3 (by analogy with interferon alpha + ribavirin combination therapy and pending the results of ongoing trials).

- Peginterferon alpha-2a based

Peginterferon alpha-2a 180 µg/wk + ribavirin 1000-1200 mg qd for 48 weeks in genotypes 1 and 4.

Peginterferon alpha-2a 180 µg/wk + ribavirin 800 mg qd for 24 weeks in genotypes 2 and 3.

As data for genotypes 5 and 6 are lacking, it is recommended to treat as for genotype 1.

3.4. *Viral monitoring of treated patients*

- Genotype 1 : Not achieving early virological response at week 12, defined as a negative qualitative PCR or a drop of the HCV RNA level of at least 2-log10, has a very high negative predictive value for SVR in the regimens with peginterferon alpha plus ribavirin (15, 19). Patients who do not show early virological response at week 12 are very unlikely to achieve SVR, and treatment can be stopped. Accordingly we recommend the following guidelines :

– Quantitative HCV RNA at baseline
– Quantitative HCV RNA at week 12
– Qualitative HCV RNA at the end of treatment (week 48)
– Qualitative HCV RNA at 24 weeks post treatment

- Genotype 2 and 3 :

– Quantitative HCV RNA at baseline
– Qualitative HCV RNA at the end of treatment (week 24)
– Qualitative HCV RNA at 24 weeks post treatment

- Genotype 4, 5, 6 :

– Quantitative HCV RNA at baseline
– Qualitative HCV RNA at week 24 (if positive, discontinuation can be considered)
– Qualitative HCV RNA at the end of treatment (48 weeks)
– Qualitative HCV RNA at 24 weeks post treatment

Data at week 12 in these genotypes are lacking.

3.5. *Treatment of acute hepatitis C*

Acute hepatitis C generally occurs in the setting of accidental exposure to infected body fluids but is rarely diagnosed. When acute infection is confirmed with or without increase of transaminases, treatment usually prevents chronicity (20,21). Accordingly, treatment is warranted. Timing and type of regimen to use are not yet clearly defined. It is strongly recommended not to treat just after exposure before the appearance of markers of HCV replication (22). According to the Belgian experience (21), treatment should be offered within the first 6 weeks of diagnosis, characterized by elevated ALT and

confirmed by positive PCR, to offer the best chance to obtain a SVR.

3.6. *Contra-indications*

- Treatment with interferon (general)

– pregnancy
– inadequate contraception
– thrombopenia (< 100 x 109/L)
– leukopenia (< 1.5 x 109/L)
– severe psychiatric disease
– epilepsia
– poorly controlled diabetes
– auto-immune disease

- Treatment with Peginterferon alpha-2b

– renal failure (creatinine clearance < 50 ml/min)

- Treatment with ribavirin

– anaemia (♀ Hb < 12 g/dL ; ♂ Hb < 13 g/dL)
– hemoglobinopathy
– renal failure (creatinine clearance < 50 ml/min)
– cardiovascular disease
– pregnancy
– inadequate contraception

During treatment and up to 7 months after treatment male patients and their female partners in fertile age should both use contraception due to the spermatotoxic and teratogenic effect of ribavirin.

4. Prevention of transmission

- Intravenous drug users

Substitution programs, needle and syringe exchange programs, educational programs (especially in correctional setting)

- Sexual transmission

– Monogamous couples do not need to use barrier protection (condoms), they should however be advised that condoms may reduce the risk of transmission
– HCV infected individuals with multiple sexual partners or in short-term relationships should be advised to use condoms to prevent HCV transmission and other sexually transmitted diseases

- Household contacts

Sharing potentially with blood contaminated items as razors and toothbrushes should be avoided

- Health care workers

– HCV infected health care workers should use standard precautions to prevent transmission and should not be restricted in their employment as proposed by the NIH Consensus Conference (9)
– Needlestick : the risk of HCV infection is estimated to be 3-10% (23). Source and exposed individual should be tested for anti-HCV. If the source is positive, HCV RNA should be determinated by qualitative assay at 2 weeks. If PCR becomes positive, weekly ALT determination should be done, and therapy should be started as soon as ALT flare appears.

- Perinatal infection : the risk is 3-12%, only when the mother is HCV RNA positive (24).

– Anti-HCV screening in pregnant mothers at risk (vide supra)
– If anti-HCV is positive HCV RNA qualitative testing should be performed.
– There are no prospective data that caesarean section prevents transmission. However, recent data suggest that the risk of contamination could be considerably lowered when elective caesarean section is performed in mothers with highly elevated viraemia (≥ 2.5 million RNA copies/mL) (25,26)
– Breast feeding does not appear to transmit hepatitis C
– Infants born to HCV RNA positive mothers should be tested for HCV infection :
– Anti-HCV after 15 months or
– HCV RNA (qualitative assay) at the age of 2-6 months

5. General measures

Abuse of alcohol and medication is to be avoided.

6. Vaccination

Vaccination against hepatitis A and B is recommended.

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