Hepatitis C virus : the burden of the disease

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Abstract

Chronic hepatitis C infection affects approximately 3% of the world population and is responsible for a large proportion of patients with cirrhosis, end-stage liver diseases, hepatocellular carcinoma and for those who are candidates for liver transplantation or die of liver-related complications.

The health care burden of this infection, whose epidemic peaked in the 1980s, is expected to significantly increase in the next 15 years in the absence of an organized national strategy.

On the other hand, hepatitis C infection can be easily diagnosed with third generation enzyme immunoassay and indications for molecular biology-based assay are well defined. Composite scores and non-invasive markers of fibrosis may in the future replace liver biopsy which is still recommended in the presence of chronically elevated transaminases and indications for antiviral treatment. (Acta gastroenterol. belg., **2002**, 65, **83-86**).

Epidemiology

Since the discovery of hepatitis C virus (HCV) in 1989, it took many years before the community realized the importance of hepatitis C.

The epidemic began in the 1940s and peaked in the 1980s and we observe now and for another 15 to 20 years its medical consequences.

HCV infection affects 300 millions people worldwide (1) i.e. 3% (0.8% in Belgium) in general and 6% (2,3) of those aged 30 to 40 years. In 2001, 10,000 people died from HCV infection in the USA (2) and 18,000 due to AIDS. As one third of HCV/HIV coinfected patients are at risk of dying of liver disease (4), we can assume that about 15,000 people died in the USA due to HCV during this year. Recent data from France (5) show that in 1997, 2,900 people died due to HCV VS 1,300 due to AIDS suggesting that the public health burden of HCV is on the rise.

If no global and national management strategy is undertaken, the perspectives for the next 15 years are worrisome : a 65%, 68% and 279% increased incidence of cirrhosis, hepatocellular carcinoma, and decompensated cirrhosis, respectively (3,6), a 528% increase of the needs for liver transplantation (3) and a 150 to 200% increase of mortality due to hepatocellular carcinoma (7). In the USA, HCV is responsible for 20% of the acute viral hepatitis, 30% of the newly diagnosed chronic liver disease (8), 30% of the cirrhosis, 60% of the hepatocellular carcinoma and 30% of the indications for liver transplantation (9).

Natural history

Twenty percent of the patients recover from acute infection whereas 80% will have persistent infection. The proportion of stable, variable or severe lifetime progression is 30%, 40% and 30% respectively (10). If we consider that all the 56 patients with potentially bad evolution are treated and that, with a combined interferon-ribavirin treatment will have a sustained response, 10% a relapse and 50% no response (11), we must expect that 30 patients of the initial 100 will have an unfavourable outcome despite therapy.

We must emphasize that, currently, only 10% of the patients requiring treatment are treated (12).

Current understanding of the natural history of HCV infection has improved with the concept of liver fibrosis progression (13). Based on the METAVIR scoring system (14), median time from infection to cirrhosis is estimated to be 30 years (range 10 to 50). Estimated life time risk of cirrhosis is 16% on the average (15). There is an almost linear correlation for fibrosis stage with age at biopsy and duration of infection and such correlation is not observed with activity grades (16).

Factors associated with more rapid progression to cirrhosis are : age at infection above 40 years old, daily intake of more than 5 drinks per day, male gender, duration of infection of more than 20 years, liver steatosis (due to obesity and/or excessive alcohol intake) of more than 30%, hepatitis B or HIV coinfection and smoking (16-21).

Once cirrhosis is present the rate of decompensation is 3% per year, incidence of hepatocellular carcinoma reaches 3 to 5% (22) per year and the annual mortality rate due to complications of portal hypertension and/or hepatocellular carcinoma is 2 to 5% (23-25). Once decompensation occurs, survival at 5 years is 50% in the absence of liver transplantation (26).

Clinical manifestations

As mentioned before, the clinical evolution can be acute or chronic.

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Incubation ranges from 2 to 26 weeks with a median of 6 weeks.

Symptoms including fatigue, loss of appetite, muscle and joint pain, right upper quadrant pain, anorexia or jaundice are present in 20% of the cases only.

Fatal evolution is extremely rare (27). Recovery from acute infection is associated with an increased T-cell proliferative response whereas chronic infection is marked by impaired production of gamma interferon by lymphocytes (28).

These functionally impaired CD8-positive T-cells suffer from lack of CD4 T-helper activity. In case of chronic infection, absence of hepatic symptoms is seen in the majority of the patients. Extrahepatic manifestations are, on the contrary, rather frequent (29) with a preponderance of rheumatic (arthralgia, myalgia, paresthesia) and cutaneo-mucous (pruritus, Sicca syndrome, Raynaud's phenomenon) symptoms.

Cryoglobulinemia-associated vasculitis presents with purpura, leg-ulcers, glomerulopathy, neuropathy and possibly non-Hodgkin lymphoma (30).

Rare extrahepatic manifestations include : lichen planus, porphyria cutanea tarda, thyroid dysfunction and diabetes.

Finally, several studies have shown that, even patients without cirrhosis have an impaired quality of life (31).

Methods for detection of HCV components

Serologic assays

The serological diagnosis of HCV infection is done by detecting anti HCV antibodies using an enzyme immunoassay (ELISA). Antibodies to HCV structural and non-structural proteins develop during infection, forming the basis of the assay. The third generation tests are 96% sensitive (detecting antibodies 7 to 8 weeks after infection) and 90 to 95% specific. In industrialised countries up to 25% of positives in blood donors are false positives, suggesting that confirmatory assays are necessary, either immunoblot or alternative ELISAs, in low prevalence settings.

HCV total core antigen detection by ELISA is promising (32,33) as a qualitative test (for the early detection of infection before the appearance of antibodies) or a quantitative test (for therapy monitoring). It could be an easy and cost-effective alternative to the PCR assay although with lower sensitivity (cut-off : 20 to 50,000 IU/ml).

Molecular tests include qualitative and quantitative assays using either target (PCR) or signal amplification (bDNA) (34,35). Qualitative detection of HCV nucleic acid sequences using PCR has a cut-off of 100 copies/ml (= 50 IU/ml).

It is not 100% sensitive because of intermittent viremia (particularly in early infection) and inappropriate handling of specimens (samples should be separated and frozen within three hours).

PCR is 97 to 99% specific because of potential contaminations.

Indications include detection of HCV in seronegative blood donors, seronegative acute hepatitis (4 weeks after possible infection), cryoglobulinemia-associated symptoms, immunosuppressed patients, positive ELISA with persistent normal transaminases (to confirm resolved infection), hemodialysis setting, pretreatment evaluation and monitoring of treatment, child born from HCV positive mother.

Quantitative assays evaluate viral load with a cut-off of 1,000 copies/ml (= 600 IU/ml) for Amplicor®. They are relevant to the prognosis and possibly to the outcome of anti-HCV therapy. They may be used in the future to decide whether therapy should be stopped if there is failure to achieve a ≥ 2 log drop in HCV RNA at 12 weeks (36).

HCV has considerable nucleotide diversity which has been classified into six distinctive genotypes.

Genotypic assays are useful for differentiating genotype 1 (two-third of the cases) from genotype 2 and 3 (one third of the cases). A lesser response to antiviral treatment is observed with type 1. The treatment period can be reduced down to 6 months in patients infected with non-1 genotype (37) with a lower cost and less side-effects.

Biochemical tests and scores

Classical tests evaluating underlying liver disease include liver tests. There is some parallelism between the level of transaminases and the risk of significant underlying liver fibrosis in the follow-up (38,39).

Severe fibrosis or cirrhosis may be suspected in case of ALT/AST ≥ 1, platelet count (below 150 × 10^9/L) (40) and low PT < 85% (41).

A series of composite scores including a combination of a2 macroglobulin, haptoglobin, apo A1, bilirubin, gammaglutamyl transpeptidase (42), platelets, AST/ALT ratio, prothrombin time (43) have a reasonable specificity for predicting, non-invasively, severe hepatic fibrosis or cirrhosis.

Serum fibrotic markers, especially serum hyaluronic acid seem to be clinically useful for assessing grade and stage of chronic hepatitis C (44).

Liver biopsy

Before initiation of therapy, a liver biopsy is usually performed in a patient with chronic ALT elevation in order to grade (A) and stage (F) the HCV-related chronic liver disease and detect associated lesions.

Treatment must be considered in the presence of significant (≥ A2F2) lesions. The risks and benefits of liver biopsy must be discussed with the patient. The potential severe complications (0.5%) associated with blind liver biopsy (44,45) as well as the mortality (0 to 0.01%) (46) should be kept in mind. In the presence of impaired

hemostasis, ascites, renal failure and/or if hemodynamic measurement is indicated, transvenous liver biopsy represent a good alternative. However, it is associated with a severe complications rate of 1% and a mortality rate between 0.1 and 0.5% (46).

In summary, an important burden of disease related to HCV infection will be rising for the next 15 to 20 years. While non-invasive diagnosis of HCV infection is easy, cheap and efficient, only 16 to 24% of the carriers are now detected (12,47,48) with around 10% (12) of patients treated. There is still a long way to go before the consequences of the epidemic will be controlled.

An urgent and vast national health plan must be implemented to detect 70% of the carriers and to restrain the burden of HCV disease.

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