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EDITORIAL

Hepatitis C: changing genotype distribution with important implications for patient management

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ABSTRACT

In the Netherlands an estimated 0.1 to 0.4% of the population are chronic hepatitis C (HCV) carriers (15,000 to 60,000 persons). HCV is characterised by genetic heterogeneity and six different genotypes have been identified. The distribution of HCV genotypes is relevant for the clinician, since there are important genotype-specific differences in response to interferon-α based treatment regimens. Between 1993 and 2005 a shift was observed in the Netherlands from a dominant prevalence of genotype 1 to a situation in which genotype non-1 is becoming more important.

KEYWORDS

Genotype distribution, hepatitis C, treatment responses

Since its discovery in 1989, hepatitis C has been recognised as a major worldwide public health problem. It is a life-shortening disease associated with complex and expensive morbidity and decreased quality of life. Nearly 170 million persons are infected by hepatitis C virus (HCV) worldwide (in Western Europe about 5 million).[1] In 15 to 20% of acute HCV infections, the patient recovers spontaneously, but in the large majority of cases, the disease runs a chronic course.[2] In the Netherlands an estimated 0.1 to 0.4% of the population are chronic HCV carriers (15,000 to 60,000 persons).[3] Although reported risk of disease progression in chronic hepatitis C differs in various populations, progression to liver cirrhosis is thought to occur in 20% of cases after 20 years of infection, with significant risk of decompensation (ascites, hepatocellular carcinoma and variceal bleeding).[2] In industrialised countries, HCV is held responsible for 40% of cases of end-stage liver cirrhosis, 60% of cases of hepatocellular carcinoma and 30% of liver transplants.[4] Risk factors for progressive disease are male sex, alcohol abuse, age >40 years at infection, and presence of significant fibrosis (≥F2 fibrosis score) according to histological examination of liver biopsy.[2] Recently a promising new device based on liver stiffness measurement (by transient elastography) has been developed to assess liver damage noninvasively: Fibroscan. Liver stiffness measurement results correlate strongly with biopsy findings in hepatitis C patients.[5,6]

HCV is characterised by genetic heterogeneity. On comparing the nucleotide sequences of the HCV genome, six different genotypes can be identified.[7] These genotypes differ in 30 to 35% of the nucleotide sites over the complete genome. Within the genotypes a variable number of more closely related distinct subtypes can be found that differ 15 to 20% in their nucleotide sequence.[8] HCV genotyping plays a key role in viral transmission studies and HCV epidemiology. The article by de Vries *et al.* in the current issue of the Journal yields new insights into HCV genotype distribution in the Netherlands.[9] These data are relevant for the clinician, since there are important genotype-specific differences in response to interferon-α based treatment regimens. Nowadays the standard anti-HCV treatment consists of a combination of pegylated (PEG)-interferon and ribavirin. The success of this therapy depends on both virus-related and host-related factors, such as age, histology and biochemical parameters.[10,11] HCV genotype and pretreatment serum values of HCV RNA are the most important predictive factors. In the registration trials PEG-interferon combined with ribavirin resulted in a sustained virological response (SVR) rate in 55% of patients. However patients infected with genotypes 2 or 3 demonstrated

SVR rates of 80%, while genotype 1 patients have only 44% SVR rate.[10,11] The SVR rates in genotype 4 patients vary between 55 and 69%.[12,13] All these trials evaluated a treatment period of 48 weeks that had been proven safe and effective in the PEG-interferon monotherapy trials.[14] At an earlier stage, Poynard and McHutchison had already proposed a stopping rule at 24 weeks for standard interferon treatment. The rule implicates that in patients who still exhibited detectable HCV RNA after 24 weeks of treatment, SVR would not be achieved even if antiviral treatment was continued for another 24 weeks, with the consequence that treatment should be discontinued.[15] Subsequently, viral kinetics during PEG-interferon therapy were studied. It turned out that the drop in viral load at 12 weeks has a high negative predictive value: if the patient does not reach what is known as the early virological response (EVR), defined as a drop in HCV RNA of at least 2 log after 12 weeks of treatment compared with baseline (i.e. at least 100 times decreased viral load), he will in all probability be a non-responder and the therapy can be discontinued. By this stopping rule the inconvenience and expense of unnecessary continuation of treatment can be avoided.[16,17] The assessment of a 12-week early viral response reduces antiviral treatment duration by 40 to 44% and antiviral costs by 44 to 45% compared with a full 48-week dosing.[18]

A next step in tailoring the dose and duration of PEG-interferon-ribavirin based treatment was taken by Hadziyannis. He showed that treatment should be individualised by genotype: genotype 1 infected patients generally require a treatment period of 48 weeks with a standard dose of ribavirin (SVR 52%) while genotypes 2 and 3 infected patients appear to be adequately treated with a low dose of ribavirin for only 24 weeks (SVR 84%), at least with PEG-interferon-α2a.[19] In order to further individualise the antiviral treatment, HCV RNA decline during the earliest stages of PEG-interferon-ribavirin therapy was studied. Zeuzem showed that an undetectable serum HCV RNA after four weeks of combination therapy resulted in a sustained response of 94 and 85% in genotype 2 and 3 patients, respectively.[20]

Others studied whether even shorter treatment periods can be achieved in some cases without compromising overall efficacy. In genotype 2 and 3 infected patients with a rapid virological response (HCV RNA below 600 IU/ml after four weeks of treatment), a treatment period of 16 weeks proved to be sufficient (SVR 82%).[21] In this study the SVR in HCV genotype 2 infected patients was higher than in those infected with genotype 3. This difference was mainly due to the higher relapse rate in genotype 3 infected patients with a high pretreatment viral load (>800,000 IU/ml).[21] Therefore it was suggested to treat HCV genotype 3 infected patients with a pretreatment viral load >800,000 IU/ml for a period of 24 weeks.

Mangia showed that the treatment period in genotype 2 and 3 infected patients can be shortened to 12 weeks when serum HCV RNA is negative (<50 IU/ml) after four weeks of combination therapy.[22] Although the overall SVR was better in genotype 2 infected patients than in those infected with genotype 3, the SVR response rates were similar in patients with genotype 2 and 3 who had an early virological response and who were treated for 12 or 24 weeks.[22]

Also genotype 1 infected patients with a low baseline viral load who become HCV RNA negative at week 4 may be treated for 24 weeks without compromising sustained virological response rates.[23]

These studies all confirm differences in susceptibility for PEG-interferon-ribavirin treatment between as well as within various genotypes and that these differences become clear in the first weeks of treatment. Thus HCV genotype, viral load and decline of viral load during the earliest treatment period play key roles in tailoring and optimising antiviral therapy.[24] Recently, treatment recommendations have been given by de Knegt for genotype 2 and 3, as depicted in *table 1*.[25] Genotype distribution varies geographically with genotype 1, 2 and 3 being the most prevalent in Western Europe. Considering the different treatment schedules between genotypes 1 *vs* 2 and 3, genotype distribution in the Netherlands has a significant influence on the total costs and morbidity of anti-HCV treatment.

The CIRA study is a large, double-blind, randomised controlled multicentre trial in naive chronic hepatitis C patients comparing PEG-interferon-ribavirin treatment with a triple therapy consisting of PEG-interferon, ribavirin and amantadine/placebo. In this study, HCV genotypes were determined in 391 patients, by using amplification and hybridisation of the 5' noncoding region of the genome (INNOLiPA HCV; Innogenetics S.A., Ghent, Belgium: *table 2*). A total of 177 patients (45%) were infected with genotype 1 (more than 50% with subtype 1b), while 138

Table 1. *Treatment recommendations for HCV genotype 2 and 3 infected patients*[21,22,24]

HCV genotype	Pretreatment viral load	HCV-RNA at week 4*	Treatment§ period
2	Not important	Negative	16 weeks
2	Not important	Positive	24 weeks
3	<800,000 IU/ml	Negative	16 weeks
3	<800,000 IU/ml	Positive	24 weeks
3	>800,000 IU/ml	Not important	24 weeks

*Quantitative HCV RNA test (Amplicor Monitor HCV version 2.0, Roche Molecular Systems, Mannheim, Germany; lower limit of detection of 600 IU/ml). §Treatment consists of the combination of PEG-interferon with ribavirin in a weight-based dose (800, 1000 or 1200 mg).

Table 2. *HCV genotype distribution in the Netherlands*

Population	Year of data collection	N	HCV genotype (%)			
			1	2	3	4
HCV patients[27]	1993§	62	55	18	19	6
Dialysis patients[28]	1995/1996	71	70	17	7	4
Blood donors[26]	1994§	31	58	23	16	3
HCV patients[9]	2002-2005	351	49	10	29	11
Naive HCV patients CIRA study	2000-2004	391	45	10	35	8

§Year of publication. N = total number of persons included.

patients (35%) were infected with genotype 3, almost all with subtype a. Only 38 (10%) and 30 (8%) of the patients were infected with genotype 2 and 4, respectively. These data are largely comparable with the study by de Vries *et al.*, but differ from genotype distribution data in the blood donor population in which almost 60% of the donors were infected with genotype 1 and only 16% with genotype 3.[9,26] In the early 1990s genotype distribution in Dutch chronic hepatitis C patients was found to be as follows: 55% were infected with genotype 1, 18% were infected with genotype 2 and 19% were infected with genotype 3.[26] The data from de Vries *et al.* may be criticised for several reasons: the criteria to select physicians to be invited for data contribution are not clear: only 67% of invited physicians provided some data and there was no data verification performed.[9] Also, the authors state that: 'The percentage of patients being reported by physicians from each of the provinces was according to the percentage of inhabitants of the Netherlands living in these provinces (see *table 1* of their article)'.[9] One caveat is that hepatitis C patients are not distributed over the various provinces according to the percentage of inhabitants of the Netherlands living in these provinces, but are over-represented in certain regions such as Amsterdam and surrounding areas. Also, one might hypothesise that there could be a higher relative contribution of HCV genotype non-1 in the large cities as Amsterdam, considering the higher prevalence of these non-1 genotypes in (former) intravenous drug users. Unfortunately, the authors do not provide any additional clinical information such as sex and age distribution or stage of the liver disease. Although the data presented by the Vries *et al.* may not be a reliable reflection of the true HCV genotype distribution in the Netherlands, the observed shift from genotype 1 dominant prevalence to a situation in which genotype non-1 becomes more important (see *table 2* of de Vries *et al.*) may be real.[9] This shift may have a major and beneficial impact on treatment schedules, costs and benefits of chronic hepatitis C.

It will be interesting to follow this epidemiological spread of HCV in the future. On the one hand, the prevalence of HCV genotype 1 appears to be decreasing because it is generally acquired by transfusion of blood or blood products, a transmission route that is now effectively controlled. On the other hand it could persist in the future, since it is one of the difficult-to-treat genotypes.

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