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ORIGINAL ARTICLE

Genotype distribution amongst hepatitis C patients in the Netherlands

M.J. de Vries[1*], B. te Rijdt[1], C.M.J. van Nieuwkerk[2]

[1]Roche Nederland BV, Beneluxlaan 2a, 3446 GR Woerden, the Netherlands, [2]VU Medical Centre, Department of Gastroenterology and Hepatology, PO Box 7057, 1007 MB, Amsterdam, the Netherlands, [*]corresponding author: tel.: +31 (0)348-43 81 62, fax: +31 (0)348-43 80 06, e-mail: martin.de_vries@roche.com

ABSTRACT

Background: The prevalence of the genotypes of the hepatitis C virus (HCV) differs according to geographical location. In the United States and in European countries, the majority of patients are infected with genotype 1, 2 or 3. There is a lack of data on the distribution of HCV genotypes in the Netherlands.

Methods: The current survey determined the distribution of HCV genotypes amongst recently genotyped patients seen by physicians treating hepatitis C in the Netherlands.

Results: Almost half of the 351 patients (49.3%) were infected with genotype 1. Genotype 3 was the second most dominant genotype with a prevalence of 29.3%. Genotypes 2 and 4 were found in 9.7 and 10.5% of the patients, respectively. For 61.5% of the patients (n=216), the subtype was available. For genotype 1 the prevalence of subtype 1a and 1b was very similar, while for genotype 3 a large majority of patients were infected with subtype 3a.

Conclusion: This survey gives the first estimation of the distribution of HCV genotypes amongst unselected HCV patients in the Netherlands.

KEYWORDS

Genotype, hepatitis C, subtype, the Netherlands

INTRODUCTION

Chronic hepatitis C infection is a major cause of mortality, morbidity and liver transplantation. Worldwide, an estimated 170 million people are infected with the hepatitis C virus. The virus is a positive-sense, single-stranded RNA (9.6 kb) virus of the *Flaviviridae* family and shows considerable variability in its genomic structure.[1] The commonly used classification system proposed by Simmonds *et al.* is based on this heterogeneity and classifies different genotypes with multiple subtypes on the amount of nucleotide variation.[2-4] The prevalence of the HCV genotypes differs according to geographic location.[3-5] Some genotypes such as genotypes 1, 2 and 3 show a worldwide distribution, whereas others such as 4 and 5 are relatively restricted to certain geographical regions.[5] In the United States and Europe, the majority of HCV patients are infected with genotype 1, 2 or 3.[2,4] In 1996, Blatt *et al.* determined the genotype for 6807 patients and found that genotype 1 was predominant in all regions of the United States, with a nationwide prevalence of 73%.[6] Of the patients, 14% had genotype 2 and 8% genotype 3. In recent screenings in Germany and Belgium, genotype 1 was also predominant.[7,8]

Patients infected with different genotypes respond differently to treatment. Just over 50% of patients with genotype 1 respond with a sustained viral response to a course of 48 weeks of peginterferon-α and ribavirin.[9] Genotype 4 is also considered difficult-to-treat since treatment must be given for 48 weeks. With this treatment duration, however, the majority of patients respond to therapy.[10,11] The large majority of patients with genotype 2 or 3 respond to 24 weeks of treatment.[9] In view of the differences in response rate and treatment duration, the genotype distribution is of particular importance. In the Netherlands the distribution amongst unselected HCV patients was assessed for two smaller groups of patients more than ten years ago.[12,13] The current survey was therefore performed to determine the distribution of the HCV genotypes amongst unselected, recently genotyped patients in the Netherlands.

MATERIAL AND METHODS

In the Netherlands, testing for HCV RNA and genotyping of HCV-seropositive patients is requested by hospital-

based physicians. Out of some 200 physicians in internal medicine and gastroenterology known to treat hepatitis C, a selection treating substantial numbers of patients were asked to participate in this survey. Physicians were visited by representatives of the pharmaceutical company of which two of the authors are employees and were asked to report the genotype, date of genotyping and, if available, the subtype for the five most recently genotyped HCV patients. However, as we wanted to assess the current distribution, data from before 1 January 2002 should not be reported. Physicians were asked to report only on patients for whom the genotyping had been requested by the reporters themselves and to exclude patients for whom the genotype had already been determined by a referring physician. They were asked to report data on the last five patients irrespective of whether the patient received treatment or had comorbidities. However, as patients co-infected with HIV are often treated by different physicians, participants were asked to exclude these patients. Physicians considering participation were given documentation specifying the data being collected as well as a record form to report the data. The completed form could be submitted by mail or given to the representative at a subsequent visit. Non-respondents were reminded to submit the data by the representatives at subsequent visits. Physicians who intended to participate but who did not submit the data, or for whom no subsequent visit was planned during the survey, were reminded by telephone or letter. Data collection was undertaken from September 2004 to June 2005. Physicians were offered an incentive for their participation and investment of time. To assess whether the data obtained was distributed representatively over the country, we compared the percentage of survey patients being reported by physicians from each of the provinces and the percentage of inhabitants of the Netherlands living in these provinces.[14]

RESULTS

A total of 111 physicians treating hepatitis C were asked to participate in the survey. Of these, 74 physicians provided their data (66.7%). Most physicians (n=68) reported data for five patients, while six physicians provided data for two to four patients. Results for 360 patients were reported. However, nine patients (reported by seven physicians) were excluded since genotyping had been performed before 1 January 2002. Genotyping of the 351 patients had taken place between February 2002 and June 2005. The participating physicians were based in 53 hospitals located in 11 of the 12 Dutch provinces. The only province without participants was Flevoland (*table 1*). 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 (*table 1*).[14]

Table 1. *Distribution of patients in the current survey*

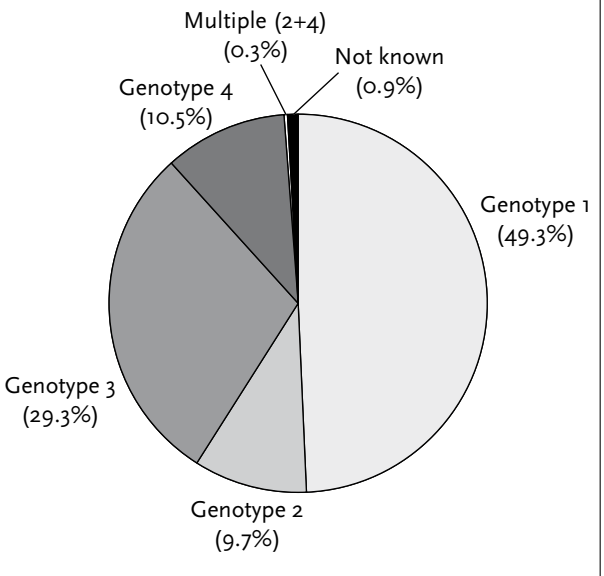
Province	No. of patients	% of the survey patients	% of Dutch inhabitants*
Flevoland	0	0	2.2
Zeeland	10	2.8	2.3
Drenthe	4	1.1	3.0
Groningen	31	8.8	3.5
Friesland	5	1.4	3.9
Overijssel	15	4.3	6.8
Limburg	37	10.5	7.0
Utrecht	42	12.0	7.1
Gelderland	38	10.8	12.1
Noord-Brabant	34	9.7	14.8
Noord-Holland	53	15.1	15.9
Zuid-Holland	82	23.4	21.2

*Statistics Netherlands, 2004.[14]

Almost half of the 351 patients (49.3%, 95% confidence interval (CI) 44.1 to 54.5%) were infected with genotype 1 (n=173) (*figure 1*). Genotype 3 was the second most dominant genotype with a prevalence of 29.3% (CI 24.6 to 34.1%, n=103). Genotypes 2 and 4 were found in 9.7% (CI 6.6 to 12.8%, n=34) and 10.5% (CI 7.3 to 13.8%, n=37) of the patients respectively. One patient showed evidence of multiple genotypes (2+4). No other genotypes were reported. For three patients, the genotype could not be determined.

For 61.5% of the patients (n=216) the subtype was available. It was not available for 35.3, 26.5, 35.0 and 67.6% of the patients with genotypes 1, 2, 3 and 4 respectively. For genotype 1, the prevalence of subtype 1a and 1b amongst

Figure 1. *Distribution of hepatitis C genotypes amongst 351 patients in the Netherlands*



the subtyped patients was 46.4 and 49.1% respectively (*table 2*). Some patients had both subtypes. The majority of the genotype 2 patients had a combination of subtypes 2a and 2b, while a large majority of genotype 3 patients had subtype 3a (94.0%). For a minority of genotype 4 patients the subtype was available, half of these patients were infected with the combination of 4c and 4d.

Table 2. *Distribution of hepatitis C subtypes amongst 351 patients in the Netherlands*

Genotype	Subtype	No.	%*
1	a	52	46.4
	b	55	49.1
	a + b	5	4.5
	Not available	61	
2	a	2	8.0
	b	8	32.0
	a + c	14	56.0
	a or c	1	4.0
	Not available	9	
3	a	63	94.0
	b	1	1.5
	c	2	3.0
	h	1	1.5
	Not available	36	
4	a	2	16.7
	c	1	8.3
	c + d	6	50.0
	e	1	8.3
	h	2	16.7
	Not available	25	
2 + 4	Not available	1	
Untypeable		3	

*Distribution of subtypes per genotype amongst subtyped patients.

DISCUSSION

This survey assesses the distribution of HCV genotypes amongst unselected HCV patients in the Netherlands by collecting data from physicians treating hepatitis C. Physicians from more than 50% of Dutch hospitals, located in 11 of the 12 provinces, participated. It can be assumed that most patients visiting a specialist for their HCV for the first time will visit a hospital in the province in which they live. The percentage of survey patients reported by physicians from each of the provinces was according to the percentage of inhabitants of the Netherlands living in these provinces (*table 1*).[14] Therefore, as long as there are no data available on regional differences in the HCV prevalence in the Netherlands, our results can be considered representative for the Netherlands. The number of patients reported by physicians from each of the provinces is too small to test for regional differences in the genotype distribution in the Netherlands.

We did not collect data on the type of assay used to determine the genotype and subtype for the patients. However, both assays used for HCV genotyping (the INNO-LiPA HCV II/VERSANT HCV Genotyping Assay (LiPA) and the Truegene HCV 5'NC Genotyping kit) can identify the six genotypes.[15] One patient showed evidence of infection with multiple genotypes. The genotype for three patients could not be determined. We do not know whether they could not be genotyped because of sensitivity problems (low viral load) or because they were infected with an unknown genotype. Nevertheless, as only three patients could not be genotyped, the validity of the data is not affected. The genotyping assays identify a large number of subtypes, but errors may occur and for a large number of patients the subtype was not available.[15] The data on the distribution of subtypes may therefore not be completely correct. Although this limitation of the survey must be taken into consideration, it has no clinical relevance as the length and the success of therapy depend on the genotype and not on the subtype.[9-11]

The distribution was assessed for HCV patients irrespective of whether treatment had been initiated. As genotypes are related significantly to the source of infection, patients with comorbidities are often infected with specific genotypes.[16] These patients could also be included; the only selection was that patients were not co-infected with HIV. A limitation of the survey is that we have no data on the number of patients with comorbidities who were included, and therefore cannot assess to what extent the results are influenced by patients from selected patient groups. However, infection with HCV in patients with comorbidities by currently known modes of transmission is nowadays excluded and most patients have been screened for HCV longer ago. We do not therefore believe that many such patients were included in the survey and hence they will not affect the results significantly.

About half of the patients were infected with genotype 1 and a third with genotype 3 (*figure 1*). Genotype 4 was found to occur at roughly the same frequency as genotype 2. This prevalence differs from that found in small groups of patients more than ten years ago, as well as from the prevalence in selected patient groups and patients with comorbidities (*table 3*).[12,13,17,18] This is to be expected as the genotype prevalence is changing over time and differs in patients with specific comorbidities.[19,20]

The data also differ from those of clinical studies in which many Dutch patients were included.[21,22] However, data from studies are for a selected group for whom treatment has been initiated and with the limitations of inclusion and exclusion criteria. In addition, patients from Belgium and Luxembourg also participated in these studies, while the prevalence of HCV genotypes may differ between countries.

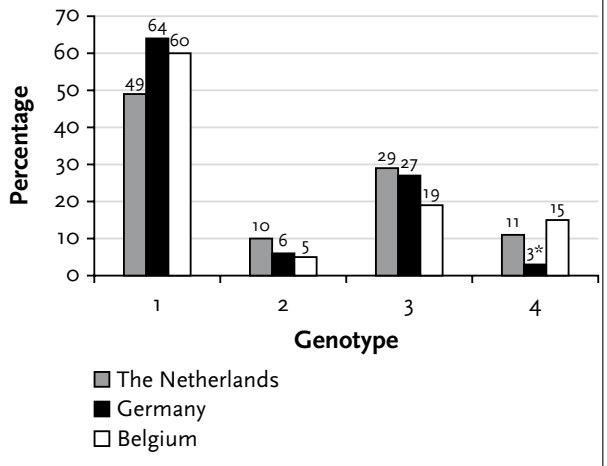
Table 3. *Distribution of hepatitis C genotypes in the Netherlands*

Patient group	Year of data collection	No.	Genotype 1 (%)	Genotype 2 (%)	Genotype 3 (%)	Genotype 4 (%)	Genotype 5 (%)	Multiple (%)
HCV patients[12]	1993+	62	55	18	19	6	-	2
HCV patients[13]	1993+	54	57	15	19	6	2	2
Dialysis patients[17]	1995-1996	71	70	17	7	4	-	6
Blood donors[18]	1994	31	58	23	16	3	-	-
Blood donors[27]	1997-2002	81	48	11	28	9	-	-
Study patients#[21]	1990-1993	322	68	10	14	5	2	1
Study patients#[22]	1996-1997	295	71	21*			8**	-
HCV patients, current survey	2002-2005	351	49	10	29	11	-	-

+Year of publication of manuscript. #Includes patients from Belgium and Luxembourg. *Genotypes 2 and 3. **Genotypes non-1,2,3.

Recent data are available for two countries bordering the Netherlands. In a screening of 2996 patients in Germany, the genotype was determined for 95.4% of the patients, while in Belgium it was determined for 265 patients.[7,8] The distribution in the Netherlands was found to be considerably different from that of Belgium and Germany (*figure 2*). The higher existence of genotype 2 in the Netherlands may be related to the presence of a large population of inhabitants from the former Dutch colony of Surinam where genotype 2 is dominant.[23] The higher presence of genotype 4 in the Netherlands and Belgium may indicate a larger immigration from Middle Eastern and Central African countries, where genotype 4 is predominant.[4,5] It was recently reported, however, that genotype 4 has become increasingly prevalent in several European countries, being prevalent in younger patients, with a short duration of infection, as well as in infected injection drug users (IDUs).[20,24] The current data indicate that the observation of 1995 that genotype 4 was found only sporadically in countries outside Africa is also outdated for the Netherlands.[4]

Figure 2. *Distribution of hepatitis C genotypes in the Netherlands, Germany and Belgium*



*Includes genotype 5 and 6. In Belgium 2% was infected with genotype 5.

Genotype 1b is mainly found amongst patients infected by blood transfusion and was the most prevalent subtype amongst genotype 1 patients in Europe in the past.[2,3,16] The majority of infected IDUs in Western countries have genotypes 1a and 3a. The current data indicate a comparable prevalence of subtypes 1a and 1b amongst genotype 1 infected patients. This may indicate that of the current HCV-genotyped patients, more have been infected by (prior) injection drug use than in the past. Indeed, surveillance of hepatitis C infection in the Netherlands indicates that injection drug use was the main route of transmission under patients diagnosed in 1999 to 2002.[25] From 1997 to 2002, a comparable prevalence of subtypes 1a and 1b was also found amongst Dutch HCV-positive, asymptomatic blood donors.[26] As the genotype distribution in voluntary blood donors, considered a low-risk population for HCV, is very similar to the distribution found amongst HCV patients in our survey, the mode of infection amongst HCV patients in general and HCV-positive blood donors may be quite similar.

In order to increase our knowledge of the transmission of HCV genotypes in the Dutch population, further research should focus on the genotype in association with epidemiological data, such as age, ethnic background, and duration and source of infection.

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