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Treatment Results of Chronic Hepatitis C Genotype 5 and 6 Infections in Germany

Therapieergebnisse für die chronische Hepatitis C mit Genotyp-5- und -6-Infektion in Deutschland

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Key words
- viral hepatitis
- hepatitis C
- HCV genotype 5
- HCV genotype 6
- HCV therapy

Schlüsselwörter
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- HCV Genotyp 5
- HCV Genotype 6
- HCV Therapie

Zusammenfassung

Infektionen mit den HCV-Genotypen 5 oder 6 sind selten und die Behandlung zumeist nicht Gegenstand kontrollierter Studien. Die Therapie dieser HCV-Genotypen wird auch in naher Zukunft auf pegyliertem Interferon und Ribavirin beruhen, da neuere Medikamente wie Boceprevir oder Telaprevir für diese Infektion nicht zugelassen sind. Für die vorliegende Arbeit wurden die Ergebnisse einer Kohortenstudie aus Deutschland ausgewertet. Die Kohorte besteht aus 23 893 Patienten. Davon waren 39 Patienten mit dem HCV Genotyp 5 (0,2 %) und 39 Patienten mit dem HCV Genotyp 6 (0,2 %) infiziert. Im Vergleich zu anderen Patienten waren Patienten mit dem HCV-Genotyp 5 älter und hatten häufiger eine Bluttransfusionen in der Anamnese. Patienten mit dem HCV-Genotyp 6 waren häufiger Asiaten und hatten höhere Werte der Alanin-Aminotransferase. Eine Therapie mit pegyliertem Interferon alpha-2a und Ribavirin begannen 24 Patienten mit dem HCV-Genotyp 5 und 27 Patienten mit dem HCV-Genotyp 6. Zum Ende der 48 Wochen Therapie war das Virus bei 79 % der Patienten mit Genotyp 5 und in 81 % Genotyp 6 Patienten nicht nachweisbar. Eine dauerhafte Elimination der Viren (sustained virologic response) erfolgte bei 58 % der Patienten mit Genotyp 5 und bei 59 % der Genotyp 6-Patienten. Zusammenfassend gilt, dass Infektionen mit den HCV-Genotypen 5 oder 6 in Deutschland selten sind. Infektionen mit Genotyp 6 wurden meist bei Migranten aus Asien diagnostiziert, die Infektionen mit Genotyp 5 traten meist spontan und lokal begrenzt auf. Das Therapieansprechen für Patienten mit HCV Genotyp 5 oder 6 ist besser als für Patienten mit den Genotypen 1 oder 4 bei gleicher Therapiedauer.

Abstract

Chronic hepatitis C due to HCV genotype 5 and 6 infection is infrequently reported and patients are usually not included in trials. As boceprevir and telaprevir are not approved for these genotypes, pegylated interferon plus ribavirin will remain the treatment of choice for the coming years. Patients infected with HCV genotype 5 or 6 were identified by data base search from an ongoing observational cohort study in Germany. Of the total 23 893 patients, 39 patients (0.2 %) carried a HCV genotype 5 and 39 patients a HCV genotype 6 (0.2 %). Compared to other genotypes patients with genotype 5 were older and more often had a history of blood transfusion. Patients with genotype 6 were more often Asian and showed higher baseline alanine transaminase. Therapy with pegylated interferon alfa-2a and ribavirin was initiated in 24 patients with HCV genotype 5 and 27 patients with HCV genotype 6. After completion of 48 weeks of therapy an end of treatment response was achieved in 79 % and 81 % of treated patients, respectively. Sustained virological response was achieved in 58 % of patients with genotype 5 and in 59 % genotype 6 patients. HCV genotype 5 and 6 infections are rare in Germany. Our findings suggest that most HCV genotype 6 infections are seen in migrants from Asia, whereas HCV genotype 5 infections seem more due to spontaneous local infections. Sustained virological response seems to be better than for patients with genotype 1 or 4 with similar treatment duration.

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Introduction

Chronic hepatitis C due to genotype 5 or 6 infection is infrequent in most parts of the world. As a consequence data assessing efficacy of pegylated interferon-based therapy in HCV genotype 5 and HCV genotype 6 infections are only available for a rather small number of patients compared to other HCV genotypes [1]. Local clusters of genotype 5 infections have been reported around the world [2, 3]. Genotype 6 infections have mainly been described in Asian and Arabian countries or Asian communities in the United States of America [4 – 7]. In general, all reports on treatment outcomes deal with low patient numbers. In particular data on treatment outcome of HCV genotype 5 are limited [2, 3, 8]. In most of the small cohorts the type of interferon and treatment duration varies. In the present study based on a large German observational cohort only patients receiving pegylated interferon alfa-2a plus ribavirin were included. Dosing and treatment duration were according to national guidelines [9].

Despite the arrival of direct acting antivirals against hepatitis C virus additional information on the efficacy of pegylated interferon alfa and ribavirin remain of interest as boceprevir and telaprevir have not been approved for treatment of HCV genotypes 5 and 6. Thus pegylated interferon alfa plus ribavirin will remain the standard therapy for HCV genotype 5 and 6 in the near future.

Methods

Patients infected with HCV genotype 5 or 6 were identified by data base search from an ongoing observational cohort study starting in March 2003; the present analysis includes 23,893 patients of whom 13,422 had been treated with pegylated interferon alfa-2a (Pegasys®, Roche Pharma AG) and ribavirin and had a complete follow-up in July 2011. Detailed characteristics of the total cohort have been published elsewhere [10]. The study was approved by health authorities and ethic committees. Due to its observational character the decision to treat a patient was at the physician's and patient's discretion. As recommended by German guidelines all patients infected with genotypes 5 and 6 were treated for 48 weeks with pegylated interferon alfa-2a 180 mcg once weekly subcutaneously plus ribavirin orally twice daily with a weight-based dose (< 75 kg 1000 mg ≥ 75 kg 1200 mg per day) [9]. Patients with genotype 1 or 4 were treated for 48 weeks with weight-based ribavirin, and patients with genotype 2 or 3 for 24 weeks.

Rapid virological response was defined as HCV RNA < 50 IU/mL 4 weeks after the start of antiviral therapy. Early virological response (EVR) was defined as an HCV RNA decay of more than 2 log or HCV RNA < 50 IU/mL 12 weeks after initiation of antiviral therapy. End of treatment response (EOT) was defined as HCV RNA < 50 IU/mL at end of therapy. Sustained virological response (SVR) was defined as HCV RNA < 50 IU/mL after 24 weeks of follow-up after end of therapy.

Results

Of total 23,893 patients screened for treatment of hepatitis C, 39 patients carried a HCV genotype 5 (0.2 %) and 39 patients a HCV genotype 6 (0.2 %) infection (**Fig. 1**). Compared to other genotypes patients with genotype 5 were older and more often had a history of blood transfusion as a likely route of HCV transmission.

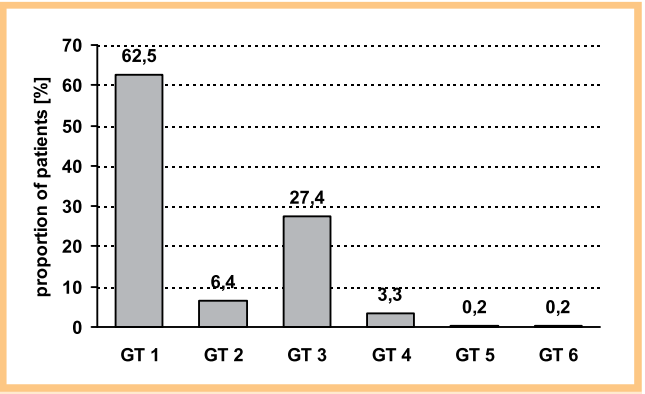

Fig. 1 Distribution of HCV genotypes in 23 893 patients of the cohort. Numbers above bars indicate percentage of patients.

Patients with genotype 6 were more often of Asian descent and showed a higher baseline alanine transaminase than patients with other genotypes.

Of all 13,422 patients receiving therapy for chronic hepatitis C in this cohort, 24 were infected by HCV genotype 5 and 27 by HCV genotype 6. Baseline demographics for all treated patients are shown in **Table 1**.

There was little difference in early virological response (EVR) between patients infected with HCV genotype 5 (100 %), genotype 6 (95 %), genotype 3 (91 %) and genotype 2 (88 %). Early virological response was lower in patients with genotype 1 (81 %) and genotype 4 (79 %) (**Table 2**). Rapid virological response was only available for a minority of patients, but generally seem to reflect the pattern observed for EVR (**Table 2**).

End of treatment response (EOT) was similar in patients infected with HCV genotype 5 (79 %), genotype 6 (81 %), genotype 3 (78 %) and genotype 2 (78 %). It was substantially lower in patients infected with genotype 1 (60 %) and genotype 4 (57 %) (**Table 2**).

Sustained virological response (SVR) in patients infected with genotype 5 was 58 % and 59 % in patients with genotype 6 infection (**Table 2**). Again as expected from the EOT results SVR was similar in patients with genotype 2 (60 %) and genotype 3 (58 %). The lowest efficacy was observed in patients with genotype 1 (42 %) or genotype 4 (44 %) infection (**Table 2**).

The proportion of premature treatment discontinuations was higher in patients infected with genotype 1 (34 %) or 4 (37 %). Premature treatment discontinuation was markedly lower in patients infected with genotype 3 (17 %), genotype 2 (14 %), genotype 5 (17 %) and genotype 6 (11 %) (**Table 2**). The main driver for the higher treatment discontinuation rates in patients infected with genotype 1 or 4 was virological failure in 18 % and 20 % of patients, respectively. The proportion of patients who discontinued due to virological failure was substantially lower in patients infected with genotypes 2, 3, 5 or 6 ranging from 2 – 7 % (**Table 2**).

Discussion

HCV genotype 5 and 6 infections are rare in Germany. Our findings suggest that most HCV genotype 6 infections are seen in migrants from Asia, whereas HCV genotype 5 infections seem more due to spontaneous local infections as patients often had a history of receiving blood products. In line with recent reports

Table 1 Baseline characteristics of patients treated for chronic hepatitis C according to HCV genotype.[1]

	GT 1	GT 2	GT 3	GT 4	GT 5	GT 6
n	7835	933	4129	474	24	27
age (years)	44 (35 – 52)	44 (36 – 52)	37 (3 – 45)	41 (34 – 46)	53 (40 – 58)	47 (37 – 52)
male	4706 (60 %)	538 (58 %)	2785 (67 %)	360 (76 %)	11 (46 %)	17 (63 %)
female	3129 (40 %)	395 (42 %)	1344 (33 %)	114 (24 %)	13 (54 %)	10 (37 %)
ethnicity						
Caucasian	6425 (85 %)	747 (84 %)	3411 (86 %)	318 (69 %)	19 (79.2 %)	9 (33.3 %)
African	59 (0.8 %)	30 (3.4 %)	19 (0.5 %)	90 (19.6 %)	1 (4.1 %)	1 (3.7 %)
Asian	99 (1.3 %)	18 (2 %)	105 (3 %)	15 (3.3 %)	–	14 (51.9 %)
Hispanic	29 (0.4 %)	5 (1 %)	16 (0.4 %)	3 (0.7 %)	–	–
unknown	916 (12.2 %)	92 (10 %)	431 (10.8 %)	34 (7.4 %)	4 (16.7 %)	3 (11.1 %)
transmission risk factor[2]						
– blood products	1488 (19 %)	156 (17 %)	317 (8 %)	35 (7 %)	12 (50 %)	3 (11 %)
– IDU	2616 (33 %)	329 (35 %)	2526 (61 %)	159 (34 %)	4 (17 %)	3 (11 %)
– other	2317 (30 %)	283 (30 %)	845 (21 %)	175 (37 %)	4 (17 %)	10 (37 %)
– unknown	1823 (23 %)	221 (24 %)	649 (16 %)	124 (26 %)	6 (25 %)	12 (44 %)
duration HCV infection (years)	10 (5 – 20)	10 (5 – 20)	9 (4 – 15)	10 (3 – 15)	18 (10 – 30)	9 (5 – 20)
baseline						
– ALT (IU/L)	73 (47 – 120)	67 (40 – 116)	92 (56 – 155)	69 (44 – 116)	74 (52 – 105)	121 (37 – 161)
– HCV RNA > 400.000 (IU/mL)	4753 (62 %)	502 (56 %)	2021 (51 %)	199 (43 %)	14 (61 %)	15 (56 %)

[1] Abbreviations: n = number of patients, GT = genotype, IDU = intravenous drug abuse, ALT = alanine transaminase, IU/L = international units per liter, HCV RNA = hepatitis C virus ribonucleic acid. Data shown as numbers (%) or median (interquartile range) where applicable.
[2] More than one risk factor could be reported per individual.

Table 2 Treatment outcome according to HCV genotype.[1]

	GT 1	GT 2	GT 3	GT 4	GT 5	GT 6
number of patients screened	14930	1543	6544	798	39	39
number of patients treated	7835	933	4129	474	24	27
duration of therapy (weeks)	48 (47 – 49)	24 (23 – 26)	24 (24 – 26)	48(46 – 48)	47 (42 – 48)	47 (47 – 48)
RVR[2]	1013/4054 (25 %)	302/419 (72 %)	1376/1862 (74 %)	110/270 (41 %)	5/7 (71 %)	5/11 (45 %)
EVR[2]	4784/1152 (81 %)	599/683 (88 %)	2616/2865 (91 %)	265/336 (79 %)	22/22 (100 %)	20/21 (95 %)
EOT	4696/7835 (60 %)	731/933 (78 %)	3203/4129 (78 %)	272/474 (57 %)	19/24 (79 %)	22/27 (81 %)
SVR	3300/7835 (42 %)	560/933 (60 %)	2377/4129 (58 %)	207/474 (44 %)	14/24 (58 %)	16/27 (59 %)
relapse	996/7835 (13 %)	97/933 (10 %)	331/4129 (8 %)	37/474 (9 %)	5/24 (21 %)	4/27 (15 %)
lost to follow up after EOT	450/7835 (6 %)	85/933 (9 %)	533/4129 (13 %)	32/474 (7 %)	0/24 (0 %)	2/27 (7 %)
all discontinuations	2672/7835 (34 %)	128/933 (14 %)	685/4129 (17 %)	173/474 (37 %)	4/24 (17 %)	3/27 (11 %)
– virological failure	1382/7835 (18 %)	15/933 (2 %)	81/4129 (2 %)	93/474 (20 %)	1/24 (4 %)	2/27 (7 %)
– adverse events	479/7835 (6 %)	35/933 (4 %)	114/4 129 (3 %)	21/474 (4 %)	1/24 (4 %)	0/27 (0 %)
– lost to follow up before EOT	403/7835 (5 %)	44/933 (5 %)	253/4 129 (6 %)	27/474 (6 %)	1/24 (4 %)	1/27 (4 %)

[1] Abbreviations: GT = genotype; RVR (rapid virologic response) = HCV-RNA < 50 IU/ml 4 weeks after the start of antiviral therapy; EVR (early virologic response) = decay more than 2 log or HCV RNA < 50 IU/ml 12 weeks after the start of antiviral therapy; EOT (end of treatment response) = HCV RNA < 50 IU/ml at the end of treatment; SVR (sustained virologic response) = HCV RNA < 50 IU/m 24 weeks after the end of antiviral therapy.
[2] RVR and EVR data not available for all patients. Data shown as numbers (%) or median (interquartile range) where applicable.

from other countries the SVR rate for treatment with pegylated interferon alfa-2a and ribavirin approaches 60 % in HCV genotype 5 and 6 patients [2, 3, 6 – 8, 11].

Recently two small comparative studies were published comparing 24-week versus 48-week treatment duration for HCV genotypes 5 and 6, respectively [6, 8]. The two studies could not detect a statistically significant difference between the two treatment durations which may be, however, at least partially due to rather low patient numbers.

The SVR rate of patients infected with genotypes 5 and 6 after 48 weeks of therapy seem to be similar to that seen in patients with HCV genotypes 2 or 3 in our cohort, which is lower than reported from studies, and superior to patients infected with genotype 1 or 4. The lower SVR rate in particular for genotype 2 patients is at least partially due to lost to follow-up during or after the end of therapy as shown in **Table 2**.

The lack of IL28B single nucleotide polymorphism data for these patients in the present study is due to the observational nature of the data base. A retrospective assessment was not possible in this setting. However given the rather small numbers of patients a meaningful evaluation of an impact of IL28B single nucleotide polymorphism on treatment outcome seems rather unlikely.

In conclusion the efficacy therapy of patients with chronic hepatitis C infected with genotype 5 or 6 in Germany seems in accordance with reports from other areas of the world. From our perspective given the moderate response rates and the significant relapse rates the results of the present study in combination with most of the literature argue against a recommendation to shorten treatment duration to 24 weeks for all patients. However an individualised approach to therapy with flexible treatment durations taking into account the rapid virologic response seems to be a feasible concept. This strategy should be validated in future trials.

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