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SPECIAL ARTICLE

Real-life costs of hepatitis C treatment

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ABSTRACT

Background: Hepatitis C virus infection is a serious health threat in today's society. Improved identification strategies have increased the number of patients undergoing the expensive treatment with ribavirin and peg-interferon, inducing a substantial economic burden.

Methods: In a retrospective cohort study in three treatment centres in the Netherlands, files of patients treated between 2001 and 2010 were systematically searched for all cost-inducing treatment details. Costs of treatment resulting in sustained viral response (SVR), relapse, non-response and the costs per cured patient were specified for genotype and treatment setting. Determinants of costs were determined by multivariate linear regression.

Results: The mean 'real-life' treatment costs excluding side effects for genotype 1/4 and genotype 2/3 were approximately € 12,900 and € 9900 for all patients, € 15,500 and € 10,100 for treatment resulting in SVR and € 16,800 and € 12,100 for relapse, respectively. Costs per cured patient were € 28,500 and € 15,400 respectively. The costs of non-response were approximately € 8000 for all genotypes. Costs of side effects can be high and are mainly caused by incidental treatment for neutropenia. Medication is the main component of treatment costs. Treatment costs were higher in the academic setting due to longer duration and higher costs of side effects. Regression analysis confirms duration as the main determinant of treatment costs excluding side effects.

Conclusion: The 'real-life' costs of treatment are mainly determined by treatment duration, medication costs and costs of side effects. The costs of unsuccessful treatment are considerable as are the costs of side effects. Therefore, future research should aim at increasing SVR rates, reducing treatment duration and preventing side effects.

KEYWORDS

Costs, hepatitis C, treatment

INTRODUCTION

Due to its serious long-term complications, hepatitis C virus (HCV) infection is increasingly recognised as a serious health threat in today's society. An estimated 123 to 170 million people have been infected globally.[1,2] In the Netherlands, this number is estimated to be between 15,000 and 60,000.[3,4] An infection with HCV leads to chronic hepatitis in 80% of cases, of which 20% develop liver cirrhosis after 20 to 30 years. Of those with cirrhosis, approximately 5% develop hepatocellular cancer.[5] As a consequence of these severe long-term complications, HCV is considered responsible for 50 to 76% of all patients with liver cancer and two-thirds of all liver transplants in the Western world.[6]

The lack of clinical signs and low awareness among the general public and medical professionals have held back detection rates considerably, but in the past decade several successful identification strategies have been developed.[7,8] This has led to an increased number of patients eligible for and undergoing treatment, causing a substantial economic burden on society. Current success rates for treatment are dependent on genotype (GT). HCV infections have been found in seven genotypes of which genotype 1 to 4 are responsible for over 98% of the infections in the Netherlands.[9,10] Of the patients infected with genotype 1 and 4, approximately 50% can attain sustained viral response (SVR), which means the disease has been cured. The majority of patients infected with these genotypes require 48 weeks of treatment. For genotype 2 and 3 the treatment success rate is more favourable at approximately 80% after 24 weeks of treatment.[11]

Costs for HCV treatment result from several components. Direct medical costs result from professional workload, hospital costs, diagnostic testing, medication use and costs of side effects. Indirect costs result from societal burden, such as productivity losses associated with absence from work.

A national guideline for the treatment of chronic hepatitis C was developed in 2008, initiated by the Netherlands Association of Gastroenterologists and Hepatologists (Nederlandse Vereniging van Maag-Darm-Leverartsen).[12] This guideline provides recommendations for the initial evaluation, the choice of therapy and the required follow-up during and after therapy. This guideline aims to provide uniformity in treatment and a recent study has demonstrated that approximately 85% of treating medical specialists in gastroenterology, hepatology and internal medicine in the Netherlands adhere to the guidelines.[13]
The costs of treatment can diverge considerably as a result of varying treatment schedules and disease and patient characteristics. In this study we aim to assess the 'real-life' costs of successful HCV treatment, relapse after treatment, non-response and the costs per cured patient in the Netherlands. In addition, we aim to identify the most important determinants of these costs.

MATERIALS AND METHODS

A retrospective cohort study was performed in three main HCV treatment centres in the Netherlands (two academic, one non-academic). The files of patients treated for HCV between 2001 and 2010 were systematically searched for details of treatment. The cooperating treatment centres provided the files of eligible patients, according to the following exclusion criteria: treatment other than ribavirin and peg-interferon, previous HCV treatment, HIV co-infection, unclosed files (meaning not designated as fully completed by the treating physician), excessive missing data (e.g. due to change of treatment institution) and no information available on treatment outcome. The researchers checked the provided files for eligibility in the study. In close cooperation with the treating physicians, the data were extracted anonymously from the electronic and paper patient files. In these files all cost-inducing elements were systematically extracted. These include the number of consultations, admissions to the hospital and length of stay, medication use, number and type of diagnostic tests performed, use of specialised homecare (e.g. 'Pegassist' or 'HepaZorg') and other registered use of hospital facilities. Side effects were recorded based on the available reporting in patient files and additional diagnostic testing or treatment outside of the protocol related to side effects known for HCV treatment. All data from one month before the beginning of drug treatment until the evaluation of treatment success at 24 weeks after drug treatment had ended were included in the analyses. Diagnostic testing as recommended in the national protocol and performed less than one year previous to the beginning of drug treatment was also taken into account. The costs resulting from the aforementioned treatment aspects were retrieved from the financial departments of the treating centres and the Dutch Health Care Insurance Board.[14] The latter costs are standardised cost prices that are recommended for use in health economic evaluations. Indirect costs, such as absence at work due to sickness, were not included in the calculations. Hence, the current study takes a healthcare perspective and estimates costs for 2010.
Mean treatment costs were determined for the different treatment outcomes and linked to the available patient and treatment characteristics. In addition, the 'costs per cure' were calculated by dividing the sum of treatment costs of all patients by the number of patients attaining SVR. The latter provides an indication of the average investment required for curing disease in one patient. Patient and treatment characteristics include age, gender, relevant lifestyle such as known hard drug use, presence of co-infections such as HBV, genotype, liver damage based on the Metavir classification (determined by biopsy or fibroscan), treatment duration and treatment setting.[15] In addition, the theoretical costs resulting from a full term and strictly followed treatment schedule according to the national treatment protocol were calculated as background information.
To detect the most important patient and treatment characteristics determining treatment costs, we performed multivariate linear regression. This analysis was performed in two steps, the first excluding and the second including 'severity of liver damage' as a parameter in the model. The first analysis was performed for all 85 treated patients and repeated for both groups of genotypes. Since information on severity of liver damage could only be found in the files of 59 patients (40 with GT1/4 and 19 with GT2/3), the impact of this parameter on treatment costs was determined in a separate analysis.

RESULTS

From the study period, 104 patient files were provided by the three treatment centres, which were considered to match the inclusion criteria, out of an estimated 150 to 200 patients treated with peg-interferon and ribavirin. After strict application of the exclusion criteria by the research team, the files of 85 patients proved suitable for analyses. The main reasons for secondary exclusion by the researchers were a positive HIV status, unclosed files or change of treating institution. Baseline characteristics are demonstrated in

table 1. The mean costs and duration of HCV treatment and the corresponding standard deviations (SD), specified for patients with GT1/4 and GT2/3 and for treatment result, are shown in *table 2*. This table also includes costs per cure. *Figure 1* demonstrates the different treatment costs for different outcomes, specified for costs of diagnostic testing, medication, hospital costs and side effects.

We found a substantial variability in costs of side effects, which was caused by only a few patients with very high costs and therefore largely determined by chance. Therefore, the primary presentation of costs is done excluding side effects with the costs of side effects presented separately.

Costs of treatment for all patients

The mean costs of treatment for all treated patients with GT1/4, excluding costs of side effects, were approximately € 12,900 after a mean treatment duration of 223 days (31.8 weeks). Mean costs of side effects were approximately € 2200. The nature of the side effects responsible for these costs is provided in the paragraphs below.

The mean treatment costs for all patients with GT2/3, excluding costs of side effects, were approximately € 9900 after a mean treatment duration of 174 days (24.8 weeks). Mean costs of side effects were approximately € 2400.

The theoretical costs of a full-term treatment based on the national protocol were € 19,189 for GT1/4 and € 11,204 for GT2/3.

Costs of successful treatment

SVR was attained in 53% of patients with GT1/4 and 74% of patients with GT2/3.

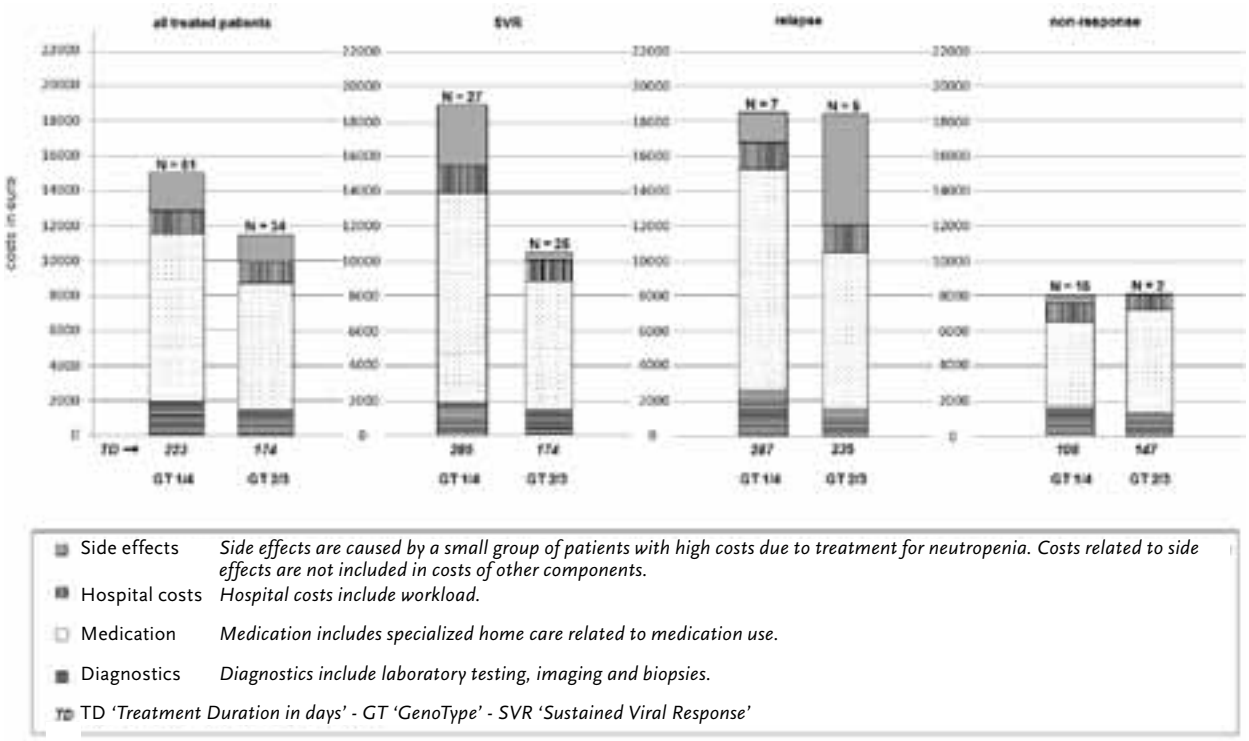
The mean costs of treatment resulting in SVR for patients with GT1/4, excluding costs of side effects, were approximately € 15,500 after a mean treatment duration of 285 days (40.7 weeks). Mean costs of side effects were approximately € 3500. The considerable costs of side effects were generated by six patients in the academic setting for whom € 5818 to € 41,543 was spent on the treatment of side effects. These high costs result from treatment with pegfilgrastim for neutropenia and epoetin alfa for anaemia.

Table 1. *Patient characteristics in different settings*

	All settings	Academic Department of Infectious Diseases	Academic Department of Gastroenterology	Non-academic Department of Infectious Diseases
Genotype 1 and 4				
Number of patients	51	15	14	22
Gender – male	40 (78%)	12 (80%)	10 (71%)	18 (82%)
Mean age	46.4	46.1	44.1	48.0
Liver damage known†	40 (78%)	14 (93%)	13 (93%)	13 (59%)
- No scarring	12 (30%)	4 (29%)	4 (31%)	4 (31%)
- Minimal scarring	7 (18%)	2 (14%)	2 (15%)	3 (23%)
- Moderate scarring	9 (23%)	3 (21%)	3 (23%)	3 (23%)
- Bridging fibrosis	6 (15%)	5 (36%)	1 (8%)	0 (0%)
- Cirrhosis or advanced scarring	6 (15%)	0 (0%)	3 (23%)	3 (23%)
Sustained viral response	27 (53%)	9 (60%)	7 (50%)	11 (50%)
Mean treatment duration in days (SD)	223 (120)	260 (144)	225 (103)	196 (110)
Genotype 2 and 3				
Number of patients	34	13	7	14
Gender – male	26 (76%)	9 (69%)	6 (86%)	11 (79%)
Mean age	42.5	39.8	48.4	42.1
Liver damage known †	19 (56%)	9 (69%)	7 (100%)	3 (21%)
- No scarring	5 (26%)	5 (56%)	0 (0%)	0 (0%)
- Minimal scarring	5 (26%)	3 (33%)	2 (29%)	0 (0%)
- Moderate scarring	4 (21%)	1 (11%)	2 (29%)	1 (33%)
- Bridging fibrosis	1 (5%)	0 (0%)	1 (14%)	0 (0%)
- Cirrhosis or advanced scarring	4 (21%)	0 (0%)	2 (29%)	2 (67%)
Sustained viral response	25 (73%)	11 (85%)	3 (43%)*	11 (79%)
Mean treatment duration in days (SD)	174 (70)	190 (69)	156 (99)*	167 (56)

***Low number due to two dropouts with early side effects; †Based on Metavir classification for liver damage; 1. no scarring, 2. minimal scarring, 3. scarring has occurred and extends outside the areas in the liver that contain blood vessels, 4. bridging fibrosis is spreading and connecting to other areas that contain fibrosis, 5. cirrhosis or advanced scarring of the liver.[15]**

Figure 1. *Components of costs of treatment, specified for treatment outcome**



***Four patients, two with GT1/4 and two with GT2/3, stopped treatment due to side effects after a mean duration of 31.5 days and total treatment costs of 3.796 euro. These patients are only included in the 'All patients' group.**

Table 2. *Costs (€) and duration (days) of treatment – specified for treatment result*

	All patients † Mean *SD*	***SVR*** † Mean *SD*	***Relapse*** † Mean *SD*	***Non-response*** † Mean *SD*	***Costs per cure*** ‡
Genotype 1 and 4	*n=51**	*n=27*	*n=7*	*n=15*	
Costs excluding side effects	12,856	15,483	16,800	7566	24,283
	6060	*4980*	*5466*	*2840*	
Costs including side effects	15,104	19,032	18,464	8,014	28,529
	9010	*9293*	*5502*	*2833*	
Mean treatment duration in days	223	285	287	108	
	120	*90*	*94*	*53*	
Costs if national protocol completed	19,189				
Genotype 2 and 3	*n=34*	*n=25*	*n=5*	*n=2*	
Costs excluding side effects	9911	10,095	12,068	8065	13,479
	3051	*2574*	*3490*	*184*	
Costs including side effects	11,324	10,757	18,340	8078	15,400
	7175	*3392*	*16,151*	*202*	
Mean treatment duration in days	174	174	235	147	
	70	*55*	*92*	*30*	
Costs if national protocol completed	11,204				

†Mean treatment costs and mean treatment duration of patients with the indicated outcome. ‡Costs per cure were calculated by dividing the sum of treatment costs of all patients by the number of patients attaining SVR. This provides an indication of the investment made for curing disease in one patient. *Four patients, two with GT1/4 and two with GT2/3, stopped treatment due to side effects after a mean duration of 31.5 days and mean treatment costs of € 3796. These patients are only included in the 'All patients' group.

The mean costs of treatment resulting in SVR for those with GT2/3, excluding costs of side effects, were approximately € 10,100 after a mean treatment duration of 174 days (24.8 weeks). Mean costs of side effects were lower at approximately € 650.

Costs per cure for patients with GT1/4 were approximately € 28,500 including side effects and € 24,300 excluding side effects. Costs per cure for patient with GT2/3 were approximately € 15,400 including side effects and € 13,500 excluding side effects.

Costs of unsuccessful treatment

The mean costs of treatment of patients with GT1/4 resulting in relapse after initial success, excluding side effects, were € 16,800 after a treatment duration of 287 days (41.0 weeks). Mean costs of side effects were approximately € 1700. The mean costs of treatment for patients with GT1/4 resulting in non-response, excluding side effects, were € 7600 after a treatment duration of 108 days (15.4 weeks). Mean costs of side effects were approximately € 450.

The mean costs of treatment of patients with GT2/3 resulting in relapse after initial success, excluding side effects, were € 12,100 after a treatment duration of 235 days (33.6 weeks). Mean costs of side effects were approximately € 6300. These costs of side effects were high due to the treatment of one patient in the academic setting, who received filgrastim for neutropenia costing approximately € 31,000. The mean costs of treatment for patients with GT2/3 resulting in non-response, excluding side effects, were € 8100 after a treatment duration of 147 days (21.0 weeks). Mean registered costs of side effects were only € 13 in this group.

Determinants of treatment costs

As demonstrated by the aforementioned findings, costs of side effects were substantial and consequently an important component of total treatment costs. As demonstrated in *figure 1*, the primary constituent of the treatment costs was the cost of medication.

The multivariate linear regression analyses indicated that treatment duration was the sole statistically significant determinant of treatment costs in all separate analyses (p value <0.001). Genotype, gender, age, known injecting drug use, treatment setting, somatic comorbidity, psychiatric comorbidity and severity of liver damage were not independently associated with treatment costs (p value >0.05). *Tables 3* and *4* demonstrate the full results of the multivariate analyses.

Treatment setting

Table 5 provides an overview of the mean treatment costs specified for treatment setting and outcome.

Table 3. *Multivariate linear regression – determinants of treatment costs excluding side effects in a model excluding liver damage*

	Unstandardised coefficients (B)	Standardised coefficients (Beta)	P value
All patients - (n=85)			
Genotype 2	-809.6	-0.043	0.231
Genotype 3	-442.0	-0.039	0.315
Genotype 4	-11.1	-0.001	0.985
Treatment result	51.6	0.009	0.836
Gender (1=male)	289.6	0.023	0.519
Age	18.0	0.039	0.272
Treatment duration (days)	*47.4*	*0.950*	*0.000*
Known injecting drug use (1=yes)	-301.2	-0.029	0.436
Treatment setting (1=non-academic)	-494.3	-0.047	0.171
Somatic comorbidity	-556.2	-0.037	0.295
Psychiatric comorbidity	-244.5	-0.022	0.524
(Constant)	*1660.8*		*0.149*
(Explained variance – R^2)	*0.927*		
Genotype 1 and 4 - (n=51)			
Treatment result	662.7	0.108	0.082
Gender (1=male)	657.7	0.045	0.267
Age	10.7	0.022	0.596
Treatment duration (days)	*53.0*	*1.048*	*0.000*
Known injecting drug use (1=yes)	-291.5	-0.024	0.547
Treatment setting (1=non-academic)	-446.9	-0.037	0.345
Somatic comorbidity	-794.9	-0.048	0.243
Psychiatric comorbidity	-213.4	-0.017	0.665
(Constant)	*-646.9*		*0.663*
(Explained variance – R^2)	*0.946*		
Genotype 2 and 3 - (n=34)			
Treatment result	-603.3	-0.170	0.060
Gender (1=male)	504.4	0.071	0.407
Age	-2.1	-0.006	0.935
Treatment duration (days)	*36.5*	*0.838*	*0.000*
Known injecting drug use (1=yes)	68.2	0.011	0.902
Treatment setting (1=non-academic)	-419.6	-0.069	0.369
Somatic comorbidity	829.2	0.089	0.291
Psychiatric comorbidity	-763.6	-0.112	0.151
(Constant)	*4389.1*		*0.005*
(Explained variance – R^2)	*0.870*		

In the academic setting costs per cure were 33% higher for GT1/4 and 43% higher for GT2/3, than in the non-academic setting. After adjustment for costs of side effects, this difference remained at 14 and 21%. For GT2/3, this is mainly the result of the low SVR rate in one of the academic centres in which only 43% (3 out of 7) patients reached SVR. This low SVR rate was caused by two early drop-outs due to side effects and two patients who relapsed.

Table 4. *Multivariate linear regression – determinants of treatment costs excluding side effects in a model including liver damage*

	Unstandardised coefficients (B)	Standardised coefficients (Beta)	P value
All patients - (n=59)			
Genotype 2	-1319.7	-0.059	0.181
Genotype 3	-206.6	-0.016	0.757
Genotype 4	-77.3	-0.004	0.921
Treatment result	257.1	0.045	0.472
Gender (1=male)	416.5	0.033	0.483
Age	14.8	0.031	0.512
Treatment duration (days)	*49.2*	*0.986*	*0.000*
Known injecting drug use (1=yes)	-264.1	-0.023	0.602
Treatment setting (1=non-academic)	-856.3	-0.067	0.113
Somatic comorbidity	-659.5	-0.042	0.379
Psychiatric comorbidity	-190.5	-0.016	0.729
Severity of liver damage	-107.2	-0.027	0.597
(Constant)	*1359.8*		*0.376*
(Explained variance – R^2)	*0.934*		
Genotype 1 and 4 - (n= 40)			
Treatment result	845.6	0.132	0.150
Gender (1=male)	845.6	0.058	0.305
Age	9.3	0.019	0.732
Treatment duration (days)	*54.4*	*1.076*	*0.000*
Known injecting drug use (1=yes)	-358.9	-0.028	0.577
Treatment setting (1=non-academic)	-574.8	-0.043	0.370
Somatic comorbidity	-689.6	-0.039	0.524
Psychiatric comorbidity	-380.3	-0.029	0.593
Severity of liver damage	-114.9	-0.026	0.667
(Constant)	*-999.9*		*0.644*
(Explained variance – R^2)	*0.940*		
Genotype 2 and 3 - (n=19)			
Treatment result	-565.1	-0.180	0.101
Gender (1=male)	-23.4	-0.004	0.976
Age	-36.6	-0.102	0.297
Treatment duration (days)	*32.0*	*0.769*	*0.000*
Known injecting drug use (1=yes)	387.9	0.065	0.614
Treatment setting (1=non-academic)	-1091.8	-0.135	0.207
Somatic comorbidity	-291.1	-0.036	0.757
Psychiatric comorbidity	-1234.3	-0.171	0.156
Severity of liver damage	464.4	0.229	0.151
(Constant)	*5989.0*		*0.004*
(Explained variance – R^2)	*0.947*		

An additional explanation for the higher costs in the academic setting is the longer mean treatment duration. For GT1/4, the number of 'treatment days per cure' in the academic setting is 441 days *vs* 392 in the non-academic setting (difference 12%). For GT2/3 this difference is 255 *vs* 213 days (difference 20%). The highest and lowest mean number of treatment days correspond with the highest and lowest SVR rates.

The mean total costs of treatment for all patients were approximately 50% higher in the academic setting at € 17,500 *vs* € 12,000 in the non-academic setting. Adjustment for investments made for the treatment of side effects reduces this difference to approximately 25% (€ 14,100 *vs* € 11,100). This resembles the difference in treatment duration, which is also approximately 25% (243 *vs* 196). Consequently the treatment costs per day were similar at € 58.1 in the academic setting *vs* € 57.2 in the non-academic setting. For treatment leading to SVR these costs were € 54 (academic) and € 55 (non-academic).

DISCUSSION

Summary of findings

The mean 'real-life' costs for all patients treated for HCV – excluding side effects – were € 12,900 for GT 1/4 and € 9900 for GT 2/3, while costs were slightly higher for treatments resulting in SVR. Treatment resulting in relapse increased costs by approximately € 2000. Non-response costs approximately € 8000 for all genotypes. Costs per cured patient including side effects are approximately € 28,500 and € 15,400 for GT1/4 and GT2/3. Costs of side effects can be substantial and differ considerably between patients. Treatment duration and medication costs were the most important determinants of total costs. Treatment costs were generally higher in the academic setting.

The finding that the higher costs in the academic setting result from longer duration is supported by the multivariate regression analyses which demonstrate that, when corrected for treatment duration, treatment setting is not associated with costs of treatment.

The higher costs of treatment for side effects in the academic setting can in part be explained by the treatment used for anaemia. In the academic setting epoetin alfa was used in the treatment of anaemia, whereas in the non-academic setting the treatment was based on blood transfusions. The main difference in costs of side effects, however, results from the treatment of neutropenia with (peg)filgrastim. Since this treatment should only be initiated and supervised by physicians with relevant experience, availability of this specialised care in the different settings at the time of treatment could have been of influence. The readiness and possibilities to invest more in attaining SVR could be another reason for the difference in costs of side effects. However, the costs of side effects and corresponding success rates of the different settings do not reflect this. Since the number of patients generating the costs of side effects is low, the difference in costs of side effects between settings could also be due to chance. The

Table 5. *Mean treatment costs (€) and duration – specified for treatment setting and outcome*

	All patients	SVR	Relapse	Non-response	Early stop	Costs per cure
Genotype 1 and 4	***n = 51***	***n = 27***	***n = 7***	***n = 15***	***n = 2***	
Costs excluding side effects						
All patients	12,856	15,483	16,800	7566	3266	24,283
Non-academic	11,199	13,856	15,320	6000	-	22,398
Academic	14,113	16,601	17,911	9355	3266	25,580
- Gastroenterology	13,351	15,322	15,898	11,094	3486	26,702
- Infectious diseases	14,824	17,596	19,924	7036	3045	24,707
Costs including side effects						
All patients	15,104	19,032	18,464	8014	3483	28,529
Non-academic	11,929	14,535	16,985	6449	-	23,858
Academic	17,512	22,124	19,573	9802	3483	31,741
- Gastroenterology	18,320	24,789	17,331	11,094	3921	36,640 †
- Infectious diseases	16,758	20,051	21,815	8079	3045	27,930
Mean treatment duration						
All patients	223	285	287	108	21	-
Non-academic	196	250	296	84	-	-
Academic	243	309	280	135	21	-
- Gastroenterology	225	285	224	172	21	-
- Infectious diseases	260	327	336	86	21	-
Genotype 2 and 3	***n = 34***	***n = 25***	***n = 5***	***n = 2***	***n = 2***	
Costs excluding side effects						
All patients	9911	10,095	12,068	8065	4061	13,479
Non-academic	9480	9154	12,045	7935	-	12,066
Academic	10,212	10,834	12,083	8195	4061	14,589
- Gastroenterology	9701	11,125	13,203	-	4061	22,635 *
- Infect ious diseases	10,488	10,754	9843	8195	-	12,394
Costs including side effects						
All patients	11,324	10,757	18,340	8,078	4110	15,400
Non-academic	9755	9503	12,050	7935	-	12,415
Academic	12,422	11,742	22,534	8221	4110	17,745
- Gastroenterology	15,109	13,261	28,879	-	4110	35,253 *
- Infectious diseases	10,975	11,328	9843	8221		12,971
Mean treatment duration						
All patients	174	174	235	147	42	-
Non-academic	167	155	252	126	-	-
Academic	178	189	224	168	42	-
- Gastroenterology	156	168	252	-	42	-
- Infectious diseases	190	194	168	168	-	-

*** High costs due to low sustained viral response rate (43% of total n=7, including 2 early dropouts due to side effects); † High costs due to large investment in treatment of a few patients for side effects.**

readiness and possibilities to invest more in realising SVR also provides an explanation for the difference in treatment duration between the treatment settings. This is supported by the finding that longer treatment duration seemed to be related to increased success rate. Since our study was neither designed nor aimed to assess the determinants of treatment success, we did not test this relationship in detail.

A final explanation for the longer treatment duration and higher costs for side effects in the academic setting are differences in baseline characteristics of the patient populations. In general, primary care physicians choose to send patients in whom a more complicated treatment is expected to more specialised settings such as the academic centres. In addition, less specialised medical specialists sometimes refer HCV patients who are difficult to treat to more specialised treatment centres. Due to the limited number of patients for whom liver damage could be determined and the lack of information on patient characteristics which could influence treatment success (such as BMI or ethnicity), we could not test this hypothesis.

Strengths and limitations

The main strength of our study is that it provides a 'real-life' overview of the costs of treatment as performed in daily practice instead of a theoretical profile prescribed by the protocol. This leads to a daily practice-based estimation of treatment costs assessed in a 'real-life' population. Given the highly variable population treated for HCV and the various factors which could lead to treatment adjustment, we expect that our 'real-life' study provides a more reliable estimation of treatment costs than theory-based estimations.

The main limitation is that the input for our calculations is restricted to the data that are registered in the patient files. This might have led to an underestimation of true costs, due to omissions. This underestimation is likely to be most relevant for side effects, because files will only state what is substantial or complained about. Registrations of side effects based on diagnostic testing outside the protocol will only detect side effects for which additional diagnostic testing is needed. In addition, only side effects for which it was certain that they were caused by the HCV treatment were registered as being a side effect. Comorbidities existing previous to treatment and flaring up during treatment were not included because treatment could not be confirmed as the causal factor. This might lead to an underestimation of side effects and their costs. Diagnostic testing is automatically reported by the hospital systems and costs of medication were calculated based on the initiated treatment and reported changes in medication dosage. Therefore underestimation of costs for these determinants is expected to be minor.

Given the retrospective and therefore observational data collection, we had limited influence on registration of patient characteristics which are related to treatment outcome. Consequently we had incomplete knowledge of characteristics which could have provided more background on the reasons for longer treatment duration and higher costs of treatment, such as liver damage, specified psychiatric problems, BMI, race and alcohol dependency.

The fact that our data came from three treatment centres may limit the generalisability of the conclusions. However, HCV treatment is concentrated in a limited number of expertise centres and the three centres in our study cover most of the HCV treatment in the central and eastern region of the Netherlands.

Even though the costs of HCV treatment are substantial, the healthcare costs of not treating HCV are estimated to be much higher due to development of complications such as cirrhosis and hepatocellular cancer if HCV is left untreated.[16] Consequently, as demonstrated by previous studies, timely identification and treatment with HCV is likely to be cost-effective.[7,17] In addition, recent findings demonstrate increased treatment success rates, particularly for genotype 1, Even though this will initially result in higher treatment costs, it will eventually lead to further improvement of cost-effectiveness.[18-20]

As a result of the exclusion criteria, our cohort does not cover the full range of HCV patients. Consequently, our results are best applicable for HIV-negative patients undergoing primary HCV treatment. This might have led to an underestimation of the overall costs, since costs for the excluded population are expected to be somewhat higher.

CONCLUSION

The 'real-life' costs of HCV treatment are mainly determined by the costs of medication and side effects and the duration of treatment. At present, these determinants and the costs of treatment for patients who are not treated successfully lead to a substantial financial investment needed to cure one patient. To reduce costs and improve cost-effectiveness of treatment, future research should be aimed at increasing SVR rates, reducing treatment duration and preventing side effects.

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