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Real-world treatment for chronic hepatitis C infection in Germany: Analyses from drug prescription data, 2010–2015

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Background & Aims: Direct-acting antivirals (DAAs) for hepatitis C virus (HCV) have strongly improved treatment options since 2014, but it is unclear if treatment numbers have increased. We aimed to estimate the number of treatment regimens per month from 2010–2015 and the number of patients treated and cured with DAAs since 2014, as well as the associated costs.

Methods: Drug prescription data of hepatitis C virus (HCV) antivirals for patients with statutory health insurance in Germany (~85% of population) from January 2010–December 2015 were evaluated. Standard 28-day prescriptions of pegylated interferon (PegIFN) and 1st/2nd generation DAAs were combined according to treatment guidelines and analysed. Drug costs were calculated from pharmacy sales prices. Mean treatment durations/regimen from real-world data were used to calculate drug costs/regimen and numbers of DAA-treated persons in 2014/15.

Results: From January 2010–December 2015 PegIFN/ribavirin-treatments/month decreased from ~6500 to ~650. Monthly HCV-prescriptions rose with the approval of 1st generation DAAs (2011), and decreased at the end of 2013. With the approval of 2nd generation DAAs, prescriptions/month increased (peak: ~6600; March 2015), and subsequently decreased (~4000; December 2015). In 2014, ~7000 patients were treated with DAAs, and ~20,100 in 2015. Treatment costs/month were stable at 12 million EUR (2010–2011), increased to ~38 million EUR (March 2012), and peaked to 150 million EUR (March 2015). DAA-drug costs/year added up to ~664 million EUR (2014) and ~1.3 billion EUR (2015).

Conclusions: Despite an increase in DAA prescriptions, in December 2015 less persons/month were under treatment compared to January 2010, even though access to DAAs is not limited. However, yearly treatment numbers increased from 2014–2015. Under observed conditions, ~18,000 patients/year can be cured, making substantial reduction of the estimated 160,000 diagnosed patients realizable. Political commitment to achieve further reduce DAA-prices and increase treatment numbers is recommended.

Lay summary: New treatment options with all-oral second generation direct-acting antivirals (DAAs) have resulted in the potential to cure chronic hepatitis C infection, but at high costs. Analyses from HCV drug prescription data of patients with statutory health insurance in Germany from 2010–2015, showed that DAAs replaced treatments with pegylated interferon and ribavirin, but accompanied by a disproportionate rise in costs. Although the monthly number of patients under treatment did not increase over time, the total number of patients yearly treated with DAAs increased from ~7000 patients in 2014 to ~20,100 in 2015, with a trend to shorter treatment regimens. Under observed conditions ~18,000 patients can be cured yearly, making a substantial reduction of the estimated 160,000 diagnosed patients in Germany achievable.

Introduction

Hepatitis C virus (HCV) infection is a worldwide problem; chronic HCV infection is one of the leading causes of chronic liver disease, cirrhosis, and hepatocellular carcinoma.[1–3] A rising burden of HCV-related morbidity and mortality has been reported from industrialized countries due to the accumulation of patients living with HCV infection long-term.[4,5]

Recently, however, HCV therapies have evolved rapidly, leading to the potential to alter the course of the HCV epidemic over the coming years. It has been shown that effective antiviral treatment of HCV infection may prevent the development of end-stage liver disease and reduce the risk of all-cause and liver-related mortality among patients who were cured of HCV infection.[6–8] New direct-acting antiviral agents (DAAs), which omit the need for interferon treatments have been approved for treatment since 2014. Real-world data indicate that these DAAs are both highly effective and well tolerated.[9,10] With this revolution in treatment options able to cure HCV patients on a population level, it may be possible to eliminate HCV by 2030, reaching the targets set by the World Health Organization (WHO) in its global strategy on viral hepatitis.[11,12] However, the costs of these drugs are high and jeopardize health budgets.[13,14]

Keywords: Hepatitis C; HCV treatment; Direct-acting antivirals; DAAs; Drug prescription data; Health insurance data; Pharmacy sales price; Elimination.
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In Germany, the endemic levels of HCV are low, with the prevalence of HCV antibodies at 0.3%, and viremic infections in the general population at 0.2%.[15] However, a disproportionately high prevalence is seen in groups at increased risk, *e.g.* people who inject drugs (PWID),[16] HIV co-infected men who have sex with men (MSM),[17] and migrant populations from regions with a higher HCV endemicity.[18,19] A review of the global HCV prevalence estimated the number of adults with viremic HCV infection in Germany at 267,000 (144,000–432,000) persons.[1] However, only patients diagnosed with HCV can access treatment. The total number of patients with diagnosed viremic HCV infection was estimated at 160,000 (in 2012), with 4,000 new infections reported per year.[20] New infections mainly occur among PWID and MSM.[18] Genotype (GT) distribution among patients in clinical study settings ranged between 62–73% for GT1, 16–28% for GT3, 4–7% for GT2, 3–6% for GT4, and 0.5% for GT5 and 6, respectively, depending on the composition of enrolled patient groups.[9,21]

In contrast with most other European countries, all patients in Germany with chronic HCV infection are eligible for treatment, regardless of the clinical stage of liver impairment.[22,23] In addition, any drug approved in the European Union is available to patients on prescription, at least in the first six months after approval. This may change after assessment by *The Federal Joint Committee*, the highest decision-making body of the joint self-government of physicians, dentists, hospitals and health insurance funds in Germany (http://www.english.g-ba.de/). For treatment of chronic HCV infection with DAAs, the assessment carried out and the following price negotiations were positive. All DAAs were subsequently made available to patients in the statutory health insurance (SHI) system at a fixed price. In Germany, more than 70 million persons are covered by the SHI, corresponding to ~85% of the German population.

Aims of the study

We aimed to:

a) Determine the monthly number of HCV antiviral treatment regimens prescribed for patients with SHI in Germany between January 2010 and December 2015, and to describe the treatment regimens over time.
b) Approximate the number of yearly treated and cured patients in Germany since DAA approval to determine the impact of treatment on the HCV epidemic.
c) Describe monthly HCV drug treatment costs as trend over time 2010–2015, and to estimate yearly drug costs for 2014 and 2015.

Materials and methods

Data source 1. Antiviral drug prescription data and data on drug costs

Antiviral drug prescription data and associated drug costs of HCV medications from pharmacy sales prices (PSP) were provided by Insight Health™ for January 2010–December 2015. The data were collected monthly from billing centres that processed all reimbursed prescriptions from pharmacies based on the date of redemption at the counter. The provider claimed a coverage of >99% of nationwide pharmacy sales of all individuals with SHI.

The data containing monthly frequencies of prescribed packages by package size and substance and the fixed PSP per drug at the respective point in time, were extracted as spreadsheets.

Data source 2. Information on treatment duration by regimen based on real-world data from the GECCO cohort

The treatment duration (scaled in weeks per regimen) as reported in real-world data from 1,340 patients in the German hepatitis C cohort (GECCO)[9,24] was used to calibrate the drug prescription data for calculating the number of patients treated since DAA approval (Table 1).

Analyses

The analysis of the prescription data and associated drug costs was conducted in two steps:

1. Analysis of treatment regimens and number of monthly prescribed treatments 2010–2015

For this analysis, standard 28-day package size prescriptions of drugs containing the substances: pegylated interferon α (PegIFN) 2a and 2b, boceprevir (BOC), telaprevir (TVR), sofosbuvir (SOF), simeprevir (SMV), daclatasvir (DCV), ledipasvir (LDV), ombitasvir (OBV), ritonavir-boosted paritaprevir (PTVr) or dasabuvir (DSV) were combined into regimens according to German treatment recommendations in the respective periods (Table 2). The term "regimen-months" (RM) was defined as the sum of monthly prescriptions of the respective regimen.

We divided the time under observation into three periods according to changes in approval and recommendations of HCV antiviral treatment in Germany (Supplementary material). Period I (January 2010–August 2011) corresponds to the PegIFN/RBV era. Period II (September 2011–December 2013) was characterised by the approval of protease inhibitor (PI)-based triple therapy with BOC or TVR. Period III (January 2014–December 2015) started with the continuous approval of 2nd generation DAAs and the end of BOC- or TVR-based treatment recommendation.

In period II, PegIFN was attributed to PI-based triple therapies containing BOC or TVR in a standard dosage of one injection per week. All PegIFN prescriptions not attributed to triple therapy regimens were disclosed as PegIFN + RBV regimens.

In period III, 2nd generation DAA-based regimens, in particular SOF-based regimens may, but must not be combined with PegIFN.[23] We assumed the number of prescribed DAA-based regimens containing PegIFN to be low. The exact distribution of PegIFN attributable to SOF-regimens is unknown. For the analysis of the number of monthly prescribed treatments over time, we therefore ignored PegIFN as a combination partner for these regimens and counted it separately in addition to DAA-based regimens.

Table 1. Distribution of treatment durations per DAA-based regimen among patients in the German hepatitis C (GECCO) cohort (n = 1,340).

Regimen	Duration of treatment				Total
	8 weeks	12 weeks	16 weeks	24 weeks	
SOF/PegIFN/RBV	0%	100%	0%	0%	100%
SOF/RBV	0%	36%	1%	63%	100%
SOF/SIM	0%	92%	0%	8%	100%
SOF/DCV ± RBV	0%	47%	0%	53%	100%
SOF/LDV	29%	64%	0.2%	7%	100%
OBV/PTVr/DSV ± RBV	0%	100%	0%	0%	100%
OBV/PTVr/RBV	0%	87%	0%	13%	100%

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Table 2. Definition of the terms "substances", "drugs" and "regimens".

Substance	Drug	Regimen	
SMV	SMV	SOF/SMV	± RBV
DCV	DCV	SOF/DCV	± RBV
SOF	SOF	SOF	+ RBV
	SOF/LDV	LOF/LDV	± RBV
LDV			
OBV	OBV/PTVr	OBV/PTVr	+ RBV
PTV		OBV/PTVr/DSV	± RBV
DSV	DSV		

Simeprevir, SMV; sofosbuvir, SOF; daclatasvir, DCV; ledipasvir, LDV; ombitasvir, OBV; paritaprevir, PTV; ritonavir-boosted paritaprevir, PTVr; dasabuvir, DSV.

RBV was completely ignored in this analysis, because RBV is never used other than for completing a basic regimen. RBV was only included to calculate the cumulative monthly treatment costs in Fig. 1.

2. Estimation of the number of patients in the SHI system treated in period III

To estimate the total number of persons treated with DAAs in period III we calibrated the drug prescription data with information on the distribution of varying treatment durations scaled in weeks per regimen from the German GECCO cohort (data source 2). This calculation was performed separately for the years 2014 and 2015 to account for possible changes in the distribution of treatment durations per regimen over time.

To approximate the number of patients cured since 2014 we assumed a mean sustained virological response (SVR) rate of 90% for all DAA-containing regimens since 2014, based on real-world data from treatment outcomes.[9,24–26] The number of patients successfully treated with non-DAA-containing regimens was not included, due to varying treatment durations and success.

Calculation of monthly HCV drug costs over time and of costs per regimen

For the whole study period, we calculated the monthly costs of HCV drug-treatments on the basis of PSP at the respective time for each drug. To generate total yearly treatment costs per DAA-based regimen in 2014 and 2015 we considered both the PSP for each drug (except for RBV) and the mean treatment duration per DAA-based regimen as described above. Based on the total yearly expenses per substance we calculated a mean regimen price per treatment week and the costs per regimen.

All analyses were conducted with Microsoft Excel™ 2010.

Results

Treatment regimens and number of monthly prescribed treatments 2010–2015

Period I

From January 2010 to August 2011, the recommended and only available HCV treatment regimen was PegIFN/RBV (Fig. 1). At the beginning of this period, about 6500 prescribed RM were observed, which decreased to ~4700 in August 2011. During this period, a total of ~188,900 PegIFN/RBV RM were prescribed, corresponding to an average of ~5900 monthly prescribed regimens.

Period II

Between September 2011 and December 2013, up to 2,500 prescribed triple therapy RM, consisting of PegIFN/RBV with a PI (supplementary TVR or BOC) were observed, raising the overall number of RM to a maximum of ~7800 in March 2012.

Following this peak, the number decreased steadily until the end of 2013 and reached a minimum of ~3300. During this period, a total of ~35,400 triple therapy RMs containing BOC or TVR were prescribed, corresponding to an average of ~1200 monthly prescribed regimens. Out of all monthly prescribed HCV antiviral regimens, the proportion of triple therapy RMs increased from 5% (09/2011) to a maximum of 33% (03/2012), and then continuously decreased over time to 15% at the end of 2013.

In this period, persons without a triple therapy were under PegIFN/RBV, with a total of 123,600 PegIFN + RBV RM, corresponding to ~4300 monthly prescribed regimens on average, respectively.

Period III

In period III, two further peaks of monthly prescriptions were observed: in April 2014 they peaked up to ~5800 prescribed RM, mainly induced by supplementary SOF containing regimens, decreasing thereafter to a minimum of ~3.500 RM. A rise in PegIFN prescriptions was observed in parallel to the increase of SOF prescriptions between January 2014–July 2014, probably

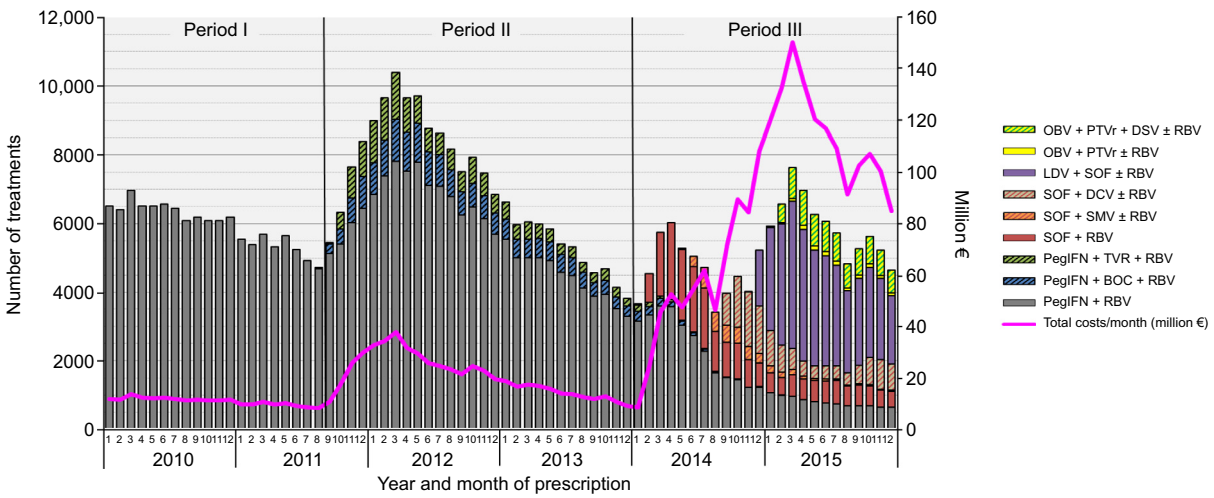

Fig. 1. Monthly prescriptions of HCV-regimens (regimen months) and total monthly HCV drug costs (01/2010–12/2015). Pegylated interferon α2a and α2b, PegIFN; ribavirin, RBV; boceprevir, BOC; telaprevir, TVR; sofosbuvir, SOF; simeprevir, SMV; daclatasvir, DCV, ledipasvir, LDV; ombitasvir, OBV; ritonavir-boosted PTV, PTVr; dasabuvir, DSV.

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due to PegIFN prescriptions being part of SOF/RBV combination regimens. A further rise of total RM due to an increase of DAA-containing regimens was observed from December 2014, with the introduction of LDV in a fixed-dose combination with SOF. We observed a rapid increase of SOF/LDV prescriptions in 2015.

Prescriptions of DCV containing regimens reached a maximum in November 2014 with ~1600 RM, followed by a subsequent steady decrease to ~360 RM in May 2015.

In January 2015, further new substances (OBV, PTVr and DSV) were introduced in the German market. In the following months, we observed an increase of monthly prescribed RM containing OBV, PTVr and DSV (±RBV) up to ~1000 RM, with a maximum in April 2015. From April 2015–December 2015, the number of OBV + PTVr + DSV ± RBV decreased steadily to ~650 RM. OBV + PTVr + RBV prescriptions without DSV remained low over the year 2015, with a maximum of ~120 RM in April 2015. Of all the prescribed DAA-RM in 2015, ~60% were LDV/SOF, ~12% were DCV containing regimens, and ~16% were OBV/PTVr ± DSV ± RBV.

The second peak in this period was observed in March 2015 with a total of ~6600 DAA-RM. Towards the end of period III the number of monthly prescriptions decreased to ~4000 RM in December 2015. In total, ~86,400 DAA-RMs were observed in period III, corresponding to an average of ~3600 monthly prescribed DAA-containing regimens.

The number of monthly PegIFN prescriptions steadily decreased from ~2700 RM in January 2014 to ~650 RM in December 2015.

Estimation of the number of patients in the SHI system treated with DAA-containing regimens in 2014 and 2015 (Table 3)

A total of ~25,500 RM of all DAA-based prescriptions in 2014 and ~60,900 RM in 2015 were recorded in the Insight Health data (Table 3). When considering the mean treatment duration per regimen derived from the GECCO cohort for each year, a total of ~7000 patients were treated with DAAs in 2014 and ~20,100 in 2015.

Most monthly prescriptions in 2014 were observed for SOF + RBV or SOF + PegIFN ± RBV, accounting for 60% (n = 15,379) of all monthly prescriptions. Accordingly, more than 60% (n = 4316) of patients treated with DAAs were prescribed SOF/RBV and SOF/PegIFN ± RBV in 2014, whereas in 2015 7% of patients received SOF/RBV and SOF/PegIFN ± RBV. In 2015, SOF/LDV accounted for 59% (n = 35,996) of all prescriptions, and was accordingly the most frequently prescribed regimen, resulting in 64% (n = 12,945) of patients treated with SOF/LDV. Additionally, in 2015 11% of patients were treated with SOF/DCV, and 16% with OBV/PTVr-based regimens, of whom n = 2958 with OBV/PTV + RBV and n = 300 with OBV/PTV/DSV ± RBV (Table 3).

When an SVR of 90% was assumed, a total of ~6300 patients in the SHI system in 2014 and ~18,100 patients in 2015 were cured with DAAs.

Monthly HCV drug costs over time

The total monthly drug costs of HCV treatments were stable at 12 million EUR/month in period I, followed by an increase to ~38 million EUR in March 2012, connected to the increase in PI-based regimens in period II. Until the end of period II, total costs decreased to below 9 million EUR/month, with the decline of RM. With the introduction of new DAAs in period III, a sharp

Table 3. Number of patients treated with DAA-based regimens and associated treatment costs (2014–2015).

DAA combination	28-day prescriptions[a]		Φ treatment weeks[b]		28-day prescriptions[a]	Φ treatment weeks[b]	Patients treated[c] (n)		Mean price/ week (€)[d]		Price/regimen (€)[e]		Total costs (€)[f]	
	2014 (n)		2014 (n)		2015 (n)	2015 (n)	2014	2015	2014	2015	2014	2015	2014	2015
SOF/PegIFN ± RBV	15,379		12,212	14,254	6,952	12,000	4,316	1,437	5,259	4,801	64,222	57,612	337,925,664	106,633,128
SOF/RBV			18,488			19,842			4,997	4,579	92,381	90,849		
SOF/SMV ± RBV	3,066		13,176		915	12,000	931	305	9,054	6,945	119,294	83,338	111,032,883	25,418,021
SOF/DCV ± RBV	5,370		18,896		7,273	13,576	1,137	2,143	8,328	7,795	157,365	105,818	178,889,056	226,760,836
SOF/LDV ± RBV	1,647		11,281		35,996	11,123	584	12,945	5,471	5,457	61,713	60,698	36,040,365	785,739,071
OBV/PTVr/DSV ± RBV	0				8,749	11,829	0	2,958		4,661	0	55,131	0	163,103,047
OBV/PTVr/RBV	0				1,027	13,714	0	300		4,247	0	58,245	0	17,446,723
Total	25,462				60,912		6,967	20,088					663,887,968	1,325,100,826

[a] Number of 28 day prescriptions per regimen (RM) (antiviral drug prescription data, provided by Insight Health™) for the years 2014 and 2015, respectively.
[b] Average duration of treatment per regimen (average number of treatment weeks per regimen) as provided by real-world data from the German GECCO cohort for the years 2014 and 2015, respectively.
[c] Twenty-eight day prescriptions*4/Ø treatment weeks.
[d] Mean pharmacy sales prices of regimens per week.
[e] Mean price/regimen per week*number of treatment weeks.
[f] Price/regimen*patients treated (n).

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increase of total monthly costs was observed, reaching a first peak in August 2014 at 62 million EUR/month, thereafter it continued to rise from September 2014–March 2015 with a maximum of more than 150 million EUR/month. After this peak, the total monthly drug costs decreased with the decline of monthly prescriptions to ~85 million EUR in December 2015 (Fig. 1).

Treatment costs per regimen and per year (2014–2015)

The overall expenses for DAA-based treatments were 663,887,968 € for 2014 and 1,325,100,826 € for 2015. The mean treatment price per week was highest for SOF/SIM in 2014 (9054 €), followed by SOF/DCV at (8323 €). In 2015 the highest mean price per week was observed for SOF/DCV (7952 €). After accounting for the treatment duration per regimen, SOF/DCV showed the highest treatment regimen costs at 157,365 € per treatment course in 2014, and 105,818 € in 2015. The mean price of a SOF/LDV regimen was slightly reduced from 61,713 € in 2014 to 60,698 € in 2015. In 2015, the mean price of OBV/PTVr/DSV ± RBV was 55,131 €, and OBV/PTVr ± RBV 58,245 €.

For regimens containing RBV, an additional ~2000 € per 12 week-prescription of 1000 mg RBV must be added to the costs of the respective regimen.

Discussion

To the best of our knowledge, this is the first description of the HCV antiviral prescription status in Germany. Over time, we observed a decrease in monthly PegIFN prescriptions and an increase of DAA prescriptions, according to the approval of new substances and to adjustments of German treatment recommendations.

A total of ~7000 persons in 2014, and of ~20,100 persons in 2015 were treated with DAA-based regimens. We consider our calculations to be robust, as other institutes such as the National Association of SHI Funds are in line with these findings.[27] Using an assumed SVR rate of 90%, a total of ~6300 patients in 2014 and ~18,100 patients in 2015 were cured from HCV with DAAs. Real-world data from German treatment registries confirm that the assumption of an overall 90% SVR is appropriate.[24–26]

However, given that there is an estimated 160,000 patients with diagnosed viremic HCV infection,[20] we would have expected a much stronger increase in monthly numbers of patients treated since the 2nd generation DAAs came onto the market, especially as DAAs can be prescribed to any HCV patient with health insurance. We presumed a minimum monthly treatment number equal to the pre-DAA era, where in 2010, ~6500 monthly treatments were observed initially. After the new increase of monthly treatment numbers at the end of 2014/beginning of 2015 we would have expected at least a steady state, but not a decrease. It is likely that, physicians have prioritized the treatment of patients with advanced disease first and have put other patients on hold.[25] In particular, patients with GT3 infection have been put on the waiting list for upcoming treatment options. The decrease in period III may be explained by unsettled cost transfer, the progress and outcome of the benefit approval and price negotiations, and medical doctors' associated fear of recourse claims. Due to these ambiguities in the reimbursement system, only a limited number of specialized medical doctors may have dared to prescribe new DAAs, resulting in a limited access to possible treatment for patients.[28]

An alternative explanation may be that the pool of diagnosed patients in care is smaller than estimated. In Germany, no HCV screening policy exists, and awareness of this infection is low. In two screening studies performed in general medicine offices and emergency rooms, only 65% and 35% of those tested positive for HCV were aware of their status, respectively.[29,30] Thus, the proportion of diagnosed persons according to Bruggmann[20] might be overestimated. We might have underestimated the number of treated patients: First, our analyses were restricted to prescription data of the SHI system, representing ~85% of the German population, and did not include prescriptions in the private sector. We assume, however, that HCV treatments in persons with private health insurance in Germany do not account for more than 10% of prescriptions, because HCV risk groups are underrepresented among privately insured persons. According to the Scientific Institute of Private Health Insurance Companies in Germany representing 70% of privately insured persons, HCV antivirals were only billed for 0.006% of privately insured persons in 2014,[31] as opposed to estimated prescriptions for 0.01% of persons in the SHI in the same year. Other patient groups not represented in the SHI system are prison inmates, who are not covered by the general SHI. HCV is highly prevalent among prisoners and need for treatment is also high, but treatment rates for people in German prisons are low.[32] Second, patient groups in clinical studies might represent a group of unknown size that needs to be included when estimating the total number of treated persons. Third, in Germany, as in other European countries, one pharmaceutical company supported the treatment of HCV patients with advanced liver disease in the frame of the European compassionate use programme (CUP) in 2014 and to a minor degree in early 2015.[33] Patients enrolled in this programme received DCV/SOF ± RBV for 24 weeks. DCV was donated by the pharmaceutical company, and SOF ± RBV were prescribed. In total, 345 patients were enrolled in the CUP in Germany in 2014,[34] leading to a small underestimation of DCV-based regimens in this year. We do not expect an impact of these missed patients in our data for the calculated total number of patients treated, since these patients were included in the category of SOF ± RBV-treated patients. Fourth, populations with higher HCV prevalence, such as PWID and migrants from high-prevalence countries might be overrepresented among people without SHI. According to an estimation by the national agency for demographic statistics, 0.1% of the population were without health insurance in 2015.[35] Since the total number of uninsured people is comparably small, we believe the impact on our calculations to be just as small.

Following a short rise in period II, a considerable decrease in total prescriptions was observed, when TVR and BOC were recommended in combination with PegIFN/RBV. These PIs raised the effectiveness of a purely PegIFN and RBV containing regimen by up to ~75–80%, but caused considerable adverse events in a high proportion of patients.[36] Accordingly, when more effective therapy options with fewer side effects became available, prescriptions of TVR and BOC decreased to zero.

In both, period II and III, we observed decreases of the number of monthly treated patients each time a new substance was awaiting approval, and increases of prescriptions of the new substance shortly after market-launch.

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In period III, we might have overestimated the number of PegIFN/RBV prescriptions. A proportion of those might have been part of a SOF/PegIFN/RBV regimen. In the GECCO cohort real-world setting, the proportion of stand-alone SOF-RBV regimens *vs.* SOF/RBV/PegIFN was approximately 1:1 (47% *vs.* 53%).[9] Hence, approximately half of SOF/RBV in our analysis might have been combined with PegIFN, reducing the monthly prescriptions of PegIFN/RBV regimens accordingly.

In all periods, a minor proportion of PegIFN treatments might have been prescribed for indications other than chronic HCV. PegIFN 2a may also be used for treatment of hepatitis B (HBV) infection and for oncologic treatment. In the SHI data, no treatment indications were reported. Yet, we might have overestimated HCV-attributed PegIFN 2a prescriptions in some cases. PegIFN treatments might also have been prescribed for acute HCV infection. Acute infection is rarely detected due to its mostly non-specific clinical course,[37] and only in settings where patients are screened regularly, *e.g.* among HIV-co-infected high risk-MSM, HCV infection might more often be detected in the acute phase. We presumed the proportion of acute infections treated with PegIFN since 2014 was very small.

In summary, to the best of our knowledge, our projection of the SHI data on the number of patients treated with DAA-based regimens since 2014 represents an accurate picture of the total number of treated HCV patients in the German SHI system. Assuming a continuing average DAA-treatment numbers of ~20,000 patients per year and steady or increasing SVR, within five to six years, 100,000 persons could be cured in Germany. This number of cured persons poses a remarkable impact on the estimated total number of diagnosed viremic patients in Germany.[1] However, to overcome the epidemic, diagnosis rates need to increase.

Costs

Over time, we observed stable total monthly costs of HCV treatments during the PegIFN/RBV period, a moderate increase with the approval of PI-based triple therapies in 2011/2012, and a sharp rise of monthly total costs in 2014, when 2nd generation DAAs were launched. However, due to differing treatment duration, the total monthly treatment costs do not allow a cost per regimen or costs per cure to be estimated. To calculate costs per regimen, we used the mean treatment duration per regimen. This analysis was only performed for period III, because of the wide range of treatment durations in periods I and II. Nonetheless even in period III costs per regimen are strongly dependent on the treatment duration. In our analysis, costs of HCV antiviral treatments in period III ranged between ~55,000 € for a OBV/PTVr/DSV regimen and ~157,500 € for a SOF/DCV regimen, without accounting for supplementary RBV. The majority of patients treated in 2015 received the both least expensive regimens SOF/LDV (~61,000 €) and OBV/PTVr/DSV (~55,000 €). Due to the high proportion of 8-week SOF/LDV regimens, this combination therapy ranged among the less costly regimens. A high proportion of patients were cured under the DAA-based regimens in period III, which may lead to the misleading conclusion that costs per SVR with DAAs correspond to the costs of a successful PegIFN/RBV treatment regimen in the pre-DAA era. Treatment costs for PegIFN/RBV regimens were estimated to range between ~10,000 and 23,400 € per patient, and for PI-based triple therapy regimens between ~33,000 and 55,000 €,[38,39] depending on the duration of treatment. However, SVR was often not reached under these regimens, therefore these costs are difficult to compare to the costs in period III. In a cost-analysis from a multicentre trial in Germany, average costs per SVR achieved under PegIFN/RBV were therefore higher and ranged between ~22,000 €/SVR and 82,000 €/SVR depending on GT and treatment experience.[40] The costs of the high proportion of unsuccessful old PegIFN/RBV treatments should not be overlooked when a price for a new successful medication is settled. Other authors have compared prices of 2nd generation DAAs globally and found significant differences across countries. They calculated the likely total costs of treating all HCV-infected patients and stated that these would have a large impact on countries' budget allocated for all medicines – some even exceed the total budget. In this context, the authors raised the question of whether medication pricing is fair to the public health.[13] A recently published paper estimated the costs of production of SOF to be significantly lower than the market price.[41]

The costs analysed in our work represent PSP. These data do not account for price reductions due to negotiations between health insurance companies and the pharmaceutical company, because this information is not open to the public. Some health insurance companies may have negotiated directly with the pharmaceutical companies to obtain lower prices for DAAs. We observed only slight price reductions in the costs for some of the DAA-based regimens from 2014 to 2015.

The SHI system allocated a special budget for HCV antivirals for SHI-patients with chronic HCV for 2015 of 1.4 billion €, and accounted the same budget for 2016.[42] In 2014, 590 million € were spent on HCV antivirals by the SHI system.[42] According to our calculations the total costs summed up to ~664 million € in 2014 and ~1.3 billion € in 2015, which fits into the allocated budget when taking into account possible price reductions that were negotiated but not controlled for in our analysis. Cost expenditures in 2015 according to a report of the National Association of SHI Funds were in line with the costs we calculated.[27]

Conclusions

We observed a moderate increase of monthly prescriptions of HCV treatment since 2010, but at lower level than expected. All highly effective substances were introduced into the German market, and access is not limited to those with advanced disease. Probable main causes for this retention to treat in a rich country with an allocated budget for reimbursement of HCV antivirals, and in a system where no prioritization of patient groups to treat is in place are the heavy prices of the new substances and ambiguities in the German reimbursement system. Further, physicians prioritize patients with advanced stages of disease. Nonetheless, yearly numbers of patients treated increased from 2014 to 2015, and under observed conditions at least ~18,000 patients can be cured from HCV per year, making a substantial reduction of the estimated 160,000 patients with diagnosed viremic infection in Germany within the coming years realizable. However, transmission and, subsequently, the number of new infections can only be reduced in the future if substantial proportions of those at risk of transmission, such as PWID, are diagnosed and treated. Also, migration from countries with higher HCV prevalence must be taken into account when aiming to eliminate the infection.

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Even if the high prices of 2nd generation DAAs were slightly reduced in 2015 as compared to 2014, still a course of treatment is only available at very high costs. We recommend strong political commitment in negotiation of discounts to achieve further price reductions and to increase the treatment numbers, also of population groups at increased risk and more difficult to reach for treatment.

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Conflict of interest

DS reports grants from HIVERA – BESTHOPE, Bio-Molecular and Epidemiological Surveillance of HIV Transmission Patterns, Transmitted Drug Resistance, Hepatitis Coinfections, and Ongoing Aging Processes in Europe, grants from MASTER HIV/HEP Molecular Surveillance and Analysis of Genetic Factors for the Optimization of Therapy and Prevention of HIV and Viral Hepatitis in Germany, grants from KokPIT study (HIV/HCV coinfection), outside the submitted work. CK: minor shareholder (<10,000 €) from patentees of pharmaceuticals described previously. PI: Advisory board: Gilead, Abbvie, ViiV, Janssen-Cilag. Speakers fees: Gilead, Abbvie, BMS, MSD, Janssen. SM: Speakers bureau: Abbvie, Bristol-Myers-Squibb, Gilead, Janssen. Advisory board: Abbvie, Bristol-Myers-Squibb, Gilead, Janssen, MSD, ViiV. RZ reports grants from Hep Epi study (situation analysis on HBV/HCV in Germany), grants from DRUCK-study (HIV/HBV/HCV among PWID), other from SPHERE-C (protocol for seroprevalence study on European level), outside the submitted work. VB reports grants from KokPIT study (HIV/HCV coinfection), grants from Hep Epi study (situation analysis on HBV/HCV in Germany), grants from DRUCK-study (HIV/HBV/HCV among IDU), other from SPHERE-C (protocol for seroprevalence study on European level), outside the submitted work. Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

CK concepted the study together with DS and RZ, managed the database and performed the data analysis with substantial contributions from DS and RZ. RZ, DS and CK interpreted the data with support from PI and SM. RZ wrote the manuscript. DS contributed to the analysis and interpretation of data and writing of the manuscript. PI and SM provided the real-world data from the German GECCO cohort and contributed to the interpretation of the results and the writing of the manuscript. VB was responsible for the design of the study and supported the writing of the manuscript. All authors critically revised the manuscript and approved the final version that was submitted.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2017.01.024.

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Author names in bold designate shared co-first authorship

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