JOURNAL OF VIRAL HEPATITIS
JVH

Journal of Viral Hepatitis, 2014, **21,** 208–215 doi:10.1111/jvh.12132

The cost of treatment failure: resource use and costs incurred by hepatitis C virus genotype 1–infected patients who do or do not achieve sustained virological response to therapy

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Received February 2013; accepted for publication May 2013

SUMMARY. Chronic hepatitis C virus (HCV) infection places a considerable economic burden on health services. Cost-effectiveness analyses of antiviral treatment for patients with chronic HCV infection are dependent on assumptions about cost reductions following sustained virological response (SVR) to therapy. This study quantified the medium-term difference in health resource usage and costs depending on treatment outcome. Retrospective chart review of patients with HCV genotype 1 infection who had received at least 2 months pegylated interferon and ribavirin therapy, with known treatment outcome was conducted. Disease status was categorized as chronic hepatitis, cirrhosis or decompensated liver disease. Health resource use was documented for each patient in each disease state. Unit costs were from the NHS 'Payment by Results' database and the British National Formulary. One hundred and ninety three patients (108 SVR, 85 non-SVR) with mean follow-up of 3.5 (SVR) and 4.9 (non-SVR) years were enrolled. No SVR patient progressed to a more severe liver disease state. Annual transition rates for non-SVR patients were 7.4% (chronic hepatitis to cirrhosis) and 4.9% (cirrhosis to decompensated liver disease). By extrapolation of modelled data over a 5-year post-treatment period, failure of patients with chronic hepatitis to achieve SVR was associated with a 13-fold increase (roughly £2300) in costs, whilst for patients who were retreated, the increase was 56-fold, equating to more than £10 000. Achievement of an SVR has significant effects on health service usage and costs. This work provides real-life data for future cost-effectiveness analyses related to the treatment for chronic HCV infection.

Keywords: antiviral therapy, chronic viral hepatitis, cost-effectiveness, health economics, hepatitis C.

An estimated 130–170 million people worldwide are chronically infected with hepatitis C virus (HCV), with around 216 000 living in the United Kingdom (UK) [1]. Chronic infection may result in progressive liver damage, leading to cirrhosis and its sequelae in at least 20–30% of individuals [2]. Both hospital admissions and deaths related to chronic HCV infection are rising in the UK [1], and end-stage liver disease resulting from chronic HCV infection is now a leading indication for liver transplantation [3]. It is estimated that by 2020, nearly 16 000 individuals will be living with HCV-related cirrhosis or hepatocellular carcinoma in England if left untreated [4]. Estimates of direct medical expenses related to HCV infection in the USA predict a rise in total expenditure to over $10 billion in the next decade [5]. The management of chronic HCV infection thus places a significant health and economic burden on national health services worldwide.

Until recently, the standard of care (SoC) for chronic HCV infection involved combination therapy with pegylated interferon and ribavirin. For genotype 1 disease, this resulted in a sustained viral response (SVR) in approximately 40–50% of patients [6], which in turn results in lower rates of liver-related morbidity and mortality [7]. Recent advances in the understanding of HCV biology have

Abbreviations: CT, computed tomography; HCV, chronic hepatitis C virus; MRI, magnetic resonance imaging; NHS, national health service; SVR, sustained virological response.

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led to the development of directly acting antiviral (DAA) agents. Two of these therapies, telaprevir and boceprevir, act on the viral NS3/4a protease and, in combination with pegylated interferon and ribavirin, have been shown to significantly improve SVR both in treatment-naïve and in treatment-experienced patients with genotype 1 disease. In the USA, triple therapy is now considered the new standard of care for patients with genotype 1 infection [8]. In England and Wales, the National Institute for Health and Clinical Excellence (NICE) has recommended the use of telaprevir or boceprevir, each in combination with pegylated interferon and ribavirin, as treatment options for genotype 1 chronic HCV infection in adults with compensated liver disease for both treatment-naïve and treatment-experienced patients [9,10].

As treatment options for genotype 1 chronic HCV infection expand, it will be important to understand the cost reductions associated with achievement of an SVR, in addition to the obvious clinical benefits to an individual patient. Previous cost-effectiveness analyses of antiviral therapy have made assumptions that achieving an SVR reduces costs [11–13]. Prior to this study, no previous paper has contrasted the resource use and costs of genotype 1 patients with and without SVR to assess the relative value of successful antiviral treatment in terms of offsetting morbidity costs.

This study aimed to compare disease progression, use of health services and costs to the UK National Health Service (NHS) between patients with genotype 1 infection who achieved an SVR following pegylated interferon and ribavirin therapy vs those who did not, using real-world data representative of routine NHS practice in the UK.

METHODS

Patients

This was a retrospective case note review conducted between May 2011 and January 2012. Patients with chronic HCV genotype 1 infection treated with pegylated interferon (either alpha 2a (Pegasys, Roche), 180 ug weekly, or alpha 2b (Viraferon PEG, Schering-Plough), 1.5 ug/kg, and ribavirin (Copegus, Roche or Rebetol, Schering-Plough given per weight according to licence), for a minimum of 2 months were eligible for the study (for the reason that failure to clear virus from shorter durations of therapy is not a treatment failure, but a failure to treat adequately). Initially, patients were identified from the Trent study of patients with chronic HCV infection, a long-term cohort study established in 1991 [14,15], which recruits patients from five centres (Derby, Leicester, Lincoln, Nottingham and Sheffield) in the East Midlands region of the UK. Subsequent additional patients who were not within the Trent database were identified in the Leicester, Lincoln and Nottingham centres. Patients who were treated after liver transplantation were excluded. Recruitment intention was to retrieve notes in chronological order of start date of treatment to ensure maximum length of follow-up, irrespective of treatment outcome. In practice, recruitment of case notes was dependent on their availability within the case note libraries at the recruitment centres.

Timelines and disease progression

The entry date into the study was defined as the date of end of treatment with pegylated interferon and ribavirin. Follow-up was until the date of data collection, death, transplantation, entry into a clinical trial using DAAs or the last visit prior to being recorded as lost to follow up. The pretreatment disease status of all patients was defined as: chronic hepatitis (absence of diagnosis of cirrhosis or decompensation), cirrhosis (diagnosed on clinical, histological or radiological grounds or by endoscopic evidence of varices) or decompensated liver disease (variceal bleed, ascites requiring treatment, hepatic encephalopathy or hepatocellular carcinoma). Dates of progression of patients after treatment to more advanced disease states (i.e. from chronic hepatitis to cirrhosis or decompensation; cirrhosis to decompensation) were recorded. Total follow-up time for each patient was the time from end of therapy to the exit date for that patient. For patients achieving an SVR, the length of follow-up was calculated by subtracting 6 months from the total follow-up time as SVR status usually became known 6 months after cessation of therapy.

Data fields

Baseline data

Patients were classified into two groups – those who achieved an SVR and those who did not (non-SVR) – on the basis of HCV RNA testing at least 6 months after the end of therapy. Data were collected using a combination of patient notes, electronic hospital records and the Trent HCV study database. Baseline data for each patient included gender, date of birth, ethnicity, risk factor for HCV acquisition, estimated duration of infection (on the assumption of infection at date of first risk exposure), pretreatment liver histology, alcohol consumption, body mass index and prior HCV treatment regimens containing nonpegylated interferon to define the characteristics of the two comparator patient groups and to allow assessment of possible confounders for the effect of SVR status on resource usage and cost post-treatment.

Resource use

On the basis of the health technology assessment of the treatment of mild chronic HCV infection [16], the following items were anticipated to be important components of any cost differences between the SVR and non-SVR patient groups: outpatient clinic visits (attended or missed), HCV

RNA tests, liver-related imaging, day-case visits (e.g. liver biopsy, endoscopy) and inpatient hospital stays. Data were captured for each separate disease state occupied by the patient, by reference to the patient case notes and hospital databases. Antiviral retreatment episodes were also recorded. Where treatment for HCV was interrupted, or there was more than one episode of treatment, resumption of therapy within 12 months after the end of initial therapy was considered as part of the initial therapy, whereas resumption of therapy after 12 months after the end of initial therapy was defined as retreatment.

Costs

Unit costs relating to these resource use items were taken from the NHS payment by results database. The main cost items were as follows: outpatient clinic visit £194; outpatient appointment not attended £50; HCV RNA test £75; ultrasound scan abdomen/liver £79; CT scan abdomen £141; MRI scan liver £245; day-case liver biopsy £322; ultrasound-guided biopsy £348; endoscopy (screening or surveillance) £142; and inpatient stay – general ward £252 per day and critical care £815. Drug costs were taken from the British National Formulary – per dose costs being Pegasys £124, Viraferon PEG £160, Copegus £13.21 and Rebetol £9.56. Data on resource use and costs were combined to give the costs of patient management for each patient.

Statistical analysis

The central tendency and distribution of continuous variables were expressed as their mean and standard deviation, respectively. Discrete variables were expressed as an absolute value or a percentage of the total. Paired t-test and Wilcoxon matched-pairs test were used to analyse the differences between the baseline characteristics of the SVR and non-SVR groups. To account for possible differences in baseline characteristics between the SVR and non-SVR groups that may have influenced subsequent health-related costs, and to obtain confidence intervals for the cost per patient, the cost data for all patients were modelled with a generalized linear model (gamma distribution, log-link function) using procedure GENMOD in SAS 9.2. (SAS Institute Inc, Cary, NC, USA)

Table 1 Baseline characteristics of study patients

	SVR	Non-SVR
Number of patients	108	85
Age at treatment in years (mean ±SD)	40.5 ± 9.7	48.0 ± 9.4
Male (%)	64.8	64.7
Caucasian (%)	85.2	88.2
IVDU (%)	63.9	50.6
BMI in kg/m^2 (mean ±SD)	26.4 ± 5.6	25.9 ± 4.4
Estimated duration of infection in years (mean ±SD)	18.2 ± 10.1	22.7 ± 9.9
Ishak stage 0/1/2 (%)	46 (66.7)	38 (52.0)
Ishak stage 3/4 (%)	14 (20.3)	14 (19.2)
Ishak stage 5/6 (%)	9 (13.0)	21 (28.8)

RESULTS

Patients

Data from 193 patients were obtained during the recruitment period, of whom 108 were classified as SVR and 85 as non-SVR. The mean follow-up observation period was 3.5 and 4.9 years for the SVR and non-SVR patients, respectively. The non-SVR group tended to be older but this did not reach significance, and had higher pretreatment Ishak stage ($P = 0.011$, Table 1).

Of the 108 SVR patients, 100 were categorized as chronic hepatitis pretreatment, six as cirrhosis and two as having had a decompensating event prior to the end of treatment. No patient who achieved an SVR transitioned between disease states over the observation period.

Of the 85 patients who did not achieve an SVR, sixty-five were categorized as chronic hepatitis pretreatment, 19 as cirrhosis and 1 had a decompensation episode prior to the end of treatment. A number of the non-SVR patients transitioned between disease states during follow-up – 17 who started as chronic hepatitis were subsequently diagnosed as cirrhotic, of whom 2 also decompensated and 2 progressed from chronic hepatitis directly to decompensation. This equates to an annual transition rate from chronic hepatitis to cirrhosis of 7.4% (Table 2). Patients who progressed had

Table 2 Rates of transition for patients who did not achieve an SVR

	Number of patients	Total follow-up (years) within disease state	Number of patients who transitioned	Rate of transition
Chronic hepatitis	65	257.88	19	7.4%/year
Cirrhosis	36*	143.27	7	4.9%/year

*Includes 19 classified as cirrhotic pretreatment plus 17 who started as chronic hepatitis pretreatment but subsequently developed cirrhosis.

more severe liver disease at initiation of therapy ($P = 0.005$) and tended to be older and more likely to be male, although these did not reach statistical significance.

In addition, seven non-SVR patients transitioned from cirrhosis pretreatment to decompensated liver disease during the post-treatment study period giving an annual transition rate of 4.9% (Table 2).

Resource usage

Forty-two of the 100 patients categorized as chronic hepatitis pretreatment who achieved an SVR were discharged from clinic coincident with the achievement of HCV RNA negativity at 6 months post-therapy. The remaining 58 were also discharged from clinic within 2 years of achievement of an SVR. No patient in this group reappeared in clinic over a mean follow-up period of 3.5 years, the assumption being therefore that there was no further progression of liver disease within this patient group over the period of follow-up. None of the remaining SVR patients (six with cirrhosis, two with decompensation) were discharged from clinic.

As retreatment of non-SVR patients incurs considerable additional resource usage and costs, the data for those patients ($n = 16$) are considered separately. Table 3 shows the resource usage for SVR and non-SVR patients who were not retreated. For patients who transitioned between disease stages, resource use was allocated according to each disease stage; hence, Table 3 contains data for 91 disease stages derived from 69 non-SVR patients.

For patients with chronic hepatitis, 20 of 21 day-case visits were for liver biopsy, with one for endoscopy. For patients with cirrhosis, 26 of 27 day-case visits were for endoscopic surveillance of oesophageal varices, with one for liver biopsy. For patients with decompensation, the majority of inpatient attendances were for the treatment for decompensated liver disease (57 days in total) with only 8 day-case endoscopies for the surveillance or treatment for oesophageal varices.

Post-therapy costs of patient management

Table 4 shows the costs incurred for the patients in the disease state chronic hepatitis and who were not retreated.

For both the SVR and non-SVR patient groups, the dominant cost was for outpatient visits (SVR – 86% of the total costs, non-SVR 79%). Inpatient costs amounted to only 1.7% of total costs for the SVR group compared with 8.5% for the non-SVR group. The cost per patient per year was £54 for the SVR group vs £506 for the non-SVR group. However, it should be noted that all of the SVR patients, but none of the non-SVR ones, were discharged from clinic. The annual cost for SVR patients will thus decline over time, as no further costs are incurred, thereby widening the gap with the costs associated with non-SVR.

Table 3 Post-treatment resource usage of patients who were not retreated

	SVR ($n = 108$)			Non-SVR ($n = 69$)		
Disease state	Chronic hep	Cirrhosis	Decomp.	Chronic hep.	Cirrhosis*	Decomp†
N	100	6	2	54	27	10
F-up (years)	351.60	26.14	4.40	197.27	103.08	17.37
Clinic visits *n*	77	52	12	409	234	63
Per patient/year	0.22	1.99	2.73	2.07	2.30	3.63
Clinic DNAs *n*	28	6	1	53	40	2
Per patient/year	0.08	0.23	0.23	0.23	0.39	0.12
USS *n*	0	28	4	37	99	13
Per patient/year	0	1.07	0.91	0.19	0.96	0.75
CT scans *n*	0	0	0	2	16	2
MRI scans *n*	0	0	0	0	3	5
HCV tests *n*	32	20	3	79	26	2
Per patient/year	0.09	0.77	0.7	0.4	0.25	0.12
Day-case visits	1‡	3§	0	21	27	5
Inpatient stay (days)	0	0	0	6	14	57

Chronic hep., chronic hepatitis; Decomp., decompensated; F-up, follow-up; Clinic DNAs, clinic appointments not attended; USS, ultrasound scans; CT, computed tomography; MRI, magnetic resonance imaging.

*14 patients were cirrhotic pretreatment, 13 transitioned into cirrhosis post-treatment.

†1 patient had decompensated disease pretreatment, 2 patients with pretreatment chronic hepatitis presented with decompensation post-treatment and 7 pretreatment cirrhotics decompensated post-treatment.

‡One patient had a liver biopsy.

§Three patients each underwent an endoscopy for surveillance of varices.

Table 4 Costs for patients with chronic hepatitis who were not retreated

	Follow-up (years)	Clinic visits	Visits DNA	HCV RNA tests	USS	CT scans	Day-case visits	Inpatient stays	Total	Cost per patient per year
SVR (n = 100)	351.6	£14938	£1400	£2400	£0	£0	£322	£0	£19060	£54
Non-SVR (n = 54)	197.3	£79346	£2650	£5925	£2923	£490	£6370	£2156	£99860	£506

The equivalent detailed costings for patients with cirrhosis or decompensation are not shown due to the small numbers of such patients. The mean annual costs for SVR patients who were cirrhotic was £556 and for those with decompensation, £663. Corresponding costs for non-SVR patients were £667 and £3394, respectively.

A generalized linear gamma model was fitted to the data to allow for the possible influence of baseline patient characteristics on costs and to obtain confidence intervals for the effect of SVR vs non-SVR on the cost per patient per year, allowing for the skewed nature of the cost variable. Disease state, gender, age, Ishak stage, ethnicity, previous treatment experience, BMI and alcohol use were included as covariates in the model, but only disease state was found to have a significant impact on the cost of the healthcare services. Thus, the final model included only treatment outcome state, disease state and their interaction term. This reduced model also has a smaller Akaike information criterion value compared with the more complex version, which indicates a better fit to the data. Table 5 shows the findings derived from the model. For patients with chronic hepatitis pretreatment, failure to achieve an SVR was associated with 10.2-fold (95% CI 6.6–15.6) higher annual costs of subsequent follow-up and management (actual £506 per patient per year vs £54; modelled £589 vs £58; $P \leq 0.05$). Healthcare costs were consistently higher in the non-SVR patients compared with patients who attained SVR, both within the subgroup of cirrhosis (ratio 1.6, 95% CI 0.5–4.9) and decompensated patients (ratio 6.1, 0.8–43.6); however, confidence intervals were wide due to the small patient numbers.

Costs associated with retreatment

Eight non-SVR patients were retreated whilst still being categorized as having chronic hepatitis, and a further eight were retreated whilst categorized as having cirrhosis. For the eight patients with chronic hepatitis, with 52.1 years of follow-up, the non-drug-related costs amounted to £41966 with a mean cost per patient per year of £806, whilst corresponding figures for the cirrhotic patients, with 39.8 years of follow-up, were £60665 and £1525, respectively. Comparable per patient per year costs for non-retreated patients were £506 (Table 4) and £677, respectively. The additional non-drug-related costs for the retreated patients were largely attributable to increased numbers of outpatient visits and HCV RNA tests related to treatment monitoring.

The duration of retreatment was very variable between patients (Table 6). Two of the eight chronic hepatitis–retreated patients achieved SVR (after 49 and 54 weeks of therapy), whilst 3 of 8 of the cirrhotic non-SVR patients also achieved SVR (after 48, 57 and 72 weeks of therapy).

Comparative costs of follow-up in all patient groups

To compare the costs of follow-up in each of the various patient groups defined by treatment response, disease state and use of retreatment, we projected costs over a 5–year follow-up period for patients in each disease stage (Table 7). For the chronic hepatitis SVR patients, this involves extrapolating the costs per patient presented in Table 4 (in which the total costs of £19060 were derived

Table 5 Cost estimates from gamma cost model for SVR vs non-SVR patients who were not retreated

	No. of patients and total follow-up in years		Cost per person year (95% confidence interval)	
Disease state	SVR	Non-SVR	SVR	Non-SVR
Chronic hepatitis	n = 100 351.60 years	n = 54 197.27 years	£58 (£45–£75)	£589 (£417–£833)
Cirrhosis	n = 6 26.14 years	n = 27 103.08 years	£586 (£207–£1655)	£914 (£560–£1491)
Decompensated	n = 2 4.40 years	n = 10 17.37 years	£719 (£119–£4347)	£4364 (£1951–£9757)

Table 6 Duration and costs of antiviral drugs in patients undergoing retreatment

Disease state in which retreatment occurred	Mean duration of retreatment in weeks (range)	Mean drug costs of retreatment (range)
Chronic hepatitis (n = 8)	30 (1–78)	£6692 (£254–£17348)
Cirrhosis (n = 8)	46 (13–98)	£9892 (£1866–£21756)

Table 7 Comparative costs per patient estimated over a 5-year period

	Outcome	Retreatment	Outpatient costs	Inpatient costs	Drug costs	Total costs
Chronic hepatitis	SVR		£187	£3	£0	£190
	Non-SVR	No	£2315	£215	£0	£2530
	Non-SVR	Yes	£3920	£110	£6692	£10722
Cirrhosis	SVR		£2700	£80	£0	£2780
	Non-SVR	No	£2984	£399	£0	£3383
	Non-SVR	Yes	£7285	£340	£9892	£17517

over a maximum 2-year period) over 5 years on the basis that postdischarge from clinic, these patients incurred no further costs (and hence, the cost for 5 years is not five times the cost per year given in Table 4). For the patients who were retreated, this allows recognition of the fact that the drug-related costs of retreatment are in effect a 'one-off' cost (i.e. they are not a recurrent annual cost). Whilst it is true that the intensity of the nondrug-related costs for these patients will increase during retreatment and is therefore not strictly speaking recurrent annual costs, the data for the actual costs were in fact accrued over a mean period of 6.5 years for the patients with chronic hepatitis and 4.9 years for the cirrhotic patients, and therefore, these figures are appropriate for 5-year projections. Of note from Table 7, the 5-year projected costs for non-cirrhotic SVR patients were thirteenfold less than for those not achieving SVR (£190 vs £2530).

DISCUSSION

This study extends the literature on the costs and cost-effectiveness of antiviral therapy for HCV. We have estimated the medium-term reduction in health service usage and costs for patients with genotype 1 infection who achieved an SVR vs those who did not. Our results suggest that for patients with chronic hepatitis pretreatment, there is at least a 10-fold difference in management costs in the 5 years following end of therapy between SVR and non-SVR patients. We are not aware of other studies that have made direct comparisons between treated patients who achieve SVR and those who do not, using real-life clinical data. A recent study from Belgium reported a doubling of management costs over a 3-year period for non-SVR vs SVR patients, but the study period included time before, during and after therapy [17]. Several other studies have addressed the cost-effectiveness of combination of pegylated interferon and ribavirin therapy [11–13,16]. Most of these have used Markov modelling to predict long-term prognosis, a fundamentally different approach to that used in this study. Furthermore, many of the published cost-effectiveness studies rely on data derived from clinical trials, which may differ substantially from real-life clinical practice, or on expert opinion, which will inevitably be less accurate than data derived from chart review. Our results are based on a large observational data set representative of patients undergoing routine NHS clinical management. The data were analysed using a multivariate statistical model to take into account possible confounding effects of baseline differences between SVR and non-SVR patients. We have shown important cost reductions arising from SVR, which previous studies have either assumed or only observed on small numbers of patients [11–13].

Chronic HCV infection is a progressive disease, leading to cirrhosis and decompensated liver disease. As costs for the management of an individual patient will depend on the underlying disease stage [17], we identified resource usage per patient within defined disease stages. We defined the timing of entry into a new, more severe, disease stage as being the time at which the patient was diagnosed by the managing physician as having reached that stage. For decompensation, this is an accurate measure, as the date of a decompensating event is known. This is not the case for cirrhosis, which may have been present for some time, perhaps years, before diagnosis. However, the date of diagnosis remains a valid starting point, as up until that date, the patient was being managed as though they had chronic hepatitis, even if, in actuality, they were cirrhotic. Other methodological limitations to our study include the following: (i) we did not attempt to record every item of resource usage, but only those of significant cost, as those will dominate the overall cost assessment. Costs will therefore be a slight underestimate, as items such as full blood counts and

liver function tests are not included. Hence, we may have underestimated the full cost reduction from SVR. (ii) Whilst we did not observe any further costs arising from SVR patients who had been discharged from clinic (all charts were reviewed up until the day of data collection, and therefore, if an SVR patient presented back to the clinic – or anywhere else in the hospital – with liver-related disease, we would have identified that event and costed it), we cannot be certain that these patients did not present elsewhere and incur costs related to their liver disease that we were not aware of. An analysis of the Scottish HCV clinical database showed that whilst patients achieving an SVR were more than four times less likely to be hospitalized or die for a liver-related reason than non-SVR patients, even non-cirrhotic SVR patients had a disproportionate burden of liver-related mortality up to six times that of the general population [8], perhaps reflecting aspects of a lifestyle associated with an increased risk of HCV infection.

To make direct comparisons between costs associated with SVR and non-SVR patients (with or without retreatment), we estimated the costs per patient over a 5-year period (Table 7). There were too few patients with advanced fibrosis pretreatment (especially for those who achieved SVR, where $n = 6$) to draw meaningful conclusions for cirrhotic patients, also bearing in mind that disease progression in such individuals is well described despite SVR [18,19]. In contrast, the data for patients with chronic hepatitis pretreatment are more robust. Failure to achieve an SVR in these patients was associated with a 13-fold increase in costs, equating roughly to an excess of £2300, whilst for a retreated patient, this escalated to a 56-fold increase in costs, equating to more than £10 000. However, these headline estimates are subject to two important methodological limitations, both of which will underestimate the true difference between costs for SVR and non-SVR patients.

Firstly, all of the SVR patients who had chronic hepatitis pretreatment were subsequently discharged from clinic within 2 years of follow-up compared with none of the equivalent non-SVR patients. Thus, the calculation of per person per annum follow-up cost for the SVR patients is not entirely logical. The longer an individual patient lives without liver disease, the higher the denominator of years of follow up, and hence, the lower the apparent annual costs will become. Thus, the gap in follow-up costs between SVR and non-SVR patients will inevitably widen over time as the former group incurs no further costs, but the latter continues to do so at an annual rate.

Secondly, no patient with pretreatment chronic hepatitis who achieved an SVR progressed into a higher disease state, which is to be expected. However, disease progression among non-SVR patients was high, with 7% of patients initially diagnosed with chronic hepatitis being subsequently diagnosed as cirrhotic, and 5% of patients with cirrhosis developing hepatic decompensation annually. These transition rates refer to a very specific group of patients (genotype 1 patients who have failed therapy with pegylated interferon and ribavirin) and therefore are not representative of patients with chronic HCV infection as a whole. Such transition rates have not been widely reported in the literature, but are crucial for understanding the long-term consequences of failed therapy. Patients whose disease progressed were older and had higher pretreatment Ishak stage scores than those who did not progress. Our data demonstrated that annual costs for patients with cirrhosis or who have undergone a decompensation event are indeed higher than those who remain in the disease stage chronic hepatitis (for non-SVR patients, annual costs of £589 vs £914 vs £4364), although as there were relatively few patients with cirrhosis ($n = 6$ SVR, 27 non-SVR) or decompensation ($n = 2$ SVR, 10 non-SVR), these comparisons should be regarded with caution. Nevertheless, progression of non-SVR patients into more expensive disease states will again increase the cost differential in management of SVR vs non-SVR patients in the mid- to long term, especially if liver transplantation is required.

The management costs for non-SVR patients who underwent retreatment were dominated by the drug costs that were significantly higher than all other aspects of patient management (Table 6). We therefore decided to analyse the costs of retreated non-SVR patients separately. The overall effect of retreatment on the cost reductions from achieving an SVR will, of course, be dependent on the retreatment rate within any particular clinical setting. The overall retreatment rate in this study was 16 of 85 (19%), 5 (31%) of whom achieved an SVR. We noted considerable between-patient variation in the duration (from 1–98 weeks) and cost of therapy (Table 6). Nontreatment-related costs were also higher for these patients than for their non-retreated counterparts, arising from increased treatment-associated visits and PCR tests.

The patterns of resource usage for patients who achieve SVR (Table 4) identify possible cost savings. For patients with pretreatment chronic hepatitis, management costs subsequent to the categorization of treatment response (i.e. a negative PCR result 6 months after the end of therapy) could be reduced to almost zero, if patients were immediately discharged from clinic and no further PCR tests conducted. This was indeed current practice for some patients, whereas others continued to attend outpatient visits and have PCR check-up 2 years later. We have focussed on the cost reductions of an SVR following therapy, but there are, of course, individual health benefits too. Future research should consider the quality of life for SVR and non-SVR patients.

In conclusion, this real-world study has quantified the effect of achievement of an SVR on health service usage and costs. The resources released in this way can help health systems meet the rising demand for effective treatment and management for patients with chronic hepatitis C. Future cost-effectiveness analyses of treatment and

prevention strategies for chronic HCV infection will able to utilize these real-life data rather than rely on assumed cost reductions for SVR.

ACKNOWLEDGEMENTS

The authors would like to thank Dr. Richard Grieve, London School of Hygiene and Tropical Medicine, for valuable discussion and advice.

DISCLOSURE

S Van Sanden, J Diels and T Ito are employees of Janssen-Cilag. KR Neal has been an advisory board member for Novartis and has received research funding from Gilead. MJ Wiselka has attended advisory boards and received speaker fees from Janssen-Cilag. WL Irving has served as a speaker, a consultant and an advisory board member for Novartis, MSD, Janssen-Cilag, Boehringer-Ingelheim, and has received research funding from Pfizer, GSK, Janssen-Cilag. The study sponsor provided support for statistical analysis. The authors had complete access to the data described within the publication.

FUNDING

This study was funded in part by Janssen-Cilag through a research grant.

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