Estimating the cost-effectiveness of 12 weeks of daclatasvir+sofosbuvir in patients chronically infected with HCV genotype 3

Phil McEwan[1,2], Thomas Ward[1], Samantha Webster[1], Anupama Kalsekar[3], Michael Brenner[4], Yong Yuan[3]

[1]Health Economics and Outcomes Research Ltd, Monmouth, United Kingdom, [2]School of Human & Health Sciences, Swansea University, Swansea, United Kingdom,
[3]World Wide Health Economics and Outcomes Research, Bristol-Myers Squibb Pharmaceuticals Ltd, Princeton, United States,
[4]UK Health Economics and Outcomes Research, Bristol-Myers Squibb Pharmaceuticals Ltd, Uxbridge, United Kingdom

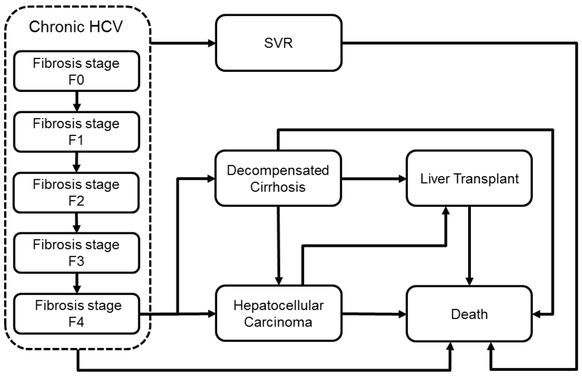
Introduction

- Chronic infection with hepatitis C virus (HCV) genotype 3 is estimated to represent 43.3% of the total HCV infection across the UK[1]. However, HCV genotype 3 is associated with increased rates of disease progression over other genotypes and is considered to be difficult to treat[2-6].
- Additionally, patients ineligible for or intolerant to interferon historically had no available treatment options, as standard of care was with pegylated interferon-alfa and ribavirin (PR)[7,8].
- The objective of this investigation was to compare the cost-effectiveness of two novel all-oral, interferon-free regimens for the treatment of patients with HCV genotype 3: daclatasvir plus sofosbuvir (DCV+SOF) and sofosbuvir plus ribavirin (SOF+RBV), applying their licensed treatment durations. A comparison to no treatment was also made for those that are ineligible for or intolerant to both interferon and ribavirin.

Methods

- A published Markov model[9-12] was used to estimate the relative cost-effectiveness of chronic hepatitis C treatments over a lifetime horizon in a cohort that had a mean age of 50 years and were 67% male[1,13-14].
- Patients were initially distributed equally across METAVIR fibrosis stages F0 to F4, and may incur disease progression through fibrosis stages and on to end-stage liver disease (ESLD) complications and death (**Figure 1**).

Figure 1: Model flow diagram



- UK specific disease state transition rates[15,16], costs[17,18] and health utility[16,19-21] estimates (**Table 1**) were utilised to inform disease progression and predict cost and quality of life outcomes.

Table 1: Disease state transition rates, costs and health utilities

Transition	Rate	Disease state	Cost (£)	Utility
F0 to F1	0.077	F0	177	0.77
F1 to F2	0.092	F1	177	0.77
F2 to F3	0.145	F2	922	0.66
F3 to F4	0.116	F3	922	0.66
F4 to DC	0.039	F4	1,464	0.55
F4/DC to HCC	0.014	DC	11,729	0.45
DC/HCC to LTx	0.030	HCC	10,452	0.45
DC to Death	0.130	LTx (Yr 1)	47,311	0.45
HCC to Death	0.430	LTx (Yr 2+)	1,781	0.67
LTx (Yr 1) to Death	0.210	Post-SVR (F0-F1)	333*	0.82
LTx (Yr 2+) to Death	0.057	Post-SVR (F2-F3)	922*	0.72
		Post-SVR (F4)	1464*	0.72

DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LTx, liver transplant; SVR, sustained virologic response; Yr, year.
* Applied in year of treatment only

- An annual discount rate of 3.5% was applied. All-cause mortality was applied in line with published UK life tables[22].
- Genotype 3 hepatitis C infection is accepted to be associated with accelerated rates of fibrosis progression; as such transition rate multipliers[2] have been applied to the transition rates presented in **Table 1** to provide a more accurate estimate of disease progression amongst this population. Rate multipliers of 1.31 and 1.44 were applied to fibrosis stage transitions and rates of progression to HCC, respectively.
- The weekly costs of DCV, SOF and RBV were £2,043.13, £2,915.24 and £66.95, respectively[23]. Clinical inputs (**Table 2**) were obtained from a matching-adjusted indirect comparison of the ALLY-3[24] and VALENCE[25] studies for DCV+SOF and SOF+RBV[26], which adjusts for baseline differences between trials.

Table 2: Therapy profiles

Regimen	Population	Duration (weeks)	SVR (%)	Regimen cost (£)
DCV+SOF	Naïve	12	96	59,500
	Experienced		83	
	IFN-ineligible*		89	
SOF+RBV	Naïve	24	94	71,572
	Experienced		79	
	IFN-ineligible*		85	
No treatment	IFN-ineligible	0	0	0

DCV, daclatasvir; IFN, interferon; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response.
* Based upon analysis of the pooled naive and experienced patients

- Cost-effectiveness was assessed through the accumulation of total costs, quality-adjusted life years (QALYs) and life years. Probabilistic sensitivity analysis was undertaken in order to assess parameter uncertainty associated with the analysis.
- Additional analysis was undertaken in order to determine the maximum reduction in SVR available before DCV+SOF became not cost-effective.

Results

- Treatment with DCV+SOF was estimated to be cost-effective against all comparators with incremental cost-effectiveness ratios ranging from -£100,287 per QALY (DCV+SOF dominating) to £7,736 per QALY (**Table 3**).

Table 3: Cost-effectiveness results

Comparison	Population	Incremental results			ICER (£/QALY)
		Costs (£)	QALYs	Life years	
DCV+SOF v SOF+RBV	Naïve	-12,904	0.129	0.069	Dominant
	Experienced	-13,702	0.242	0.152	Dominant
	IFN-ineligible	-13,382	0.197	0.119	Dominant
DCV+SOF v no treatment	IFN-ineligible	31,868	4.120	2.938	7,736

DCV, daclatasvir; ICER, incremental cost-effectiveness ratio, IFN, interferon, QALY, quality-adjusted life year; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response.

- In all comparisons of DCV+SOF to SOF+RBV, treatment with DCV+SOF was estimated to result in improved quality of life and reduced medical expenditure. QALY gains were estimated to be 0.129, 0.242 and 0.197 amongst treatment-naïve, treatment-experienced and interferon-ineligible patients, respectively. Estimated cost offsets were £12,904, £13,702 and £13,382, respectively.
- Treatment initiated with DCV+SOF in those ineligible for interferon-based therapy resulted in QALY gains of 2.938 and incremental costs of £31,868 when compared to no treatment.
- Additionally, treatment with DCV+SOF resulted in estimated life years gains of between 0.069 and 2.938 across all comparisons.
- Through probabilistic sensitivity analysis, results demonstrated that all comparisons have a 100% probability of being cost-effective at the £20,000/QALY threshold (**Figures 2 and 3**).
- In order for DCV+SOF to remain cost-effect at the £20,000/QALY threshold the SVR rate of DCV+SOF could be reduced to 84.1%, 68.4% and 75.0% when comparing to SOF+RBV in treatment naïve, treatment experienced and IFN-ineligible/intolerant populations, respectively. Against no treatment a reduction of 48.4% is possible before becoming not cost-effective.
- The largest amount of variability was observed in the comparison of DCV+SOF to no treatment, in patients ineligible for/intolerant of interferon-based therapy, due to the uncertainty surrounding disease progression and management parameters and the lack of an SVR in the comparator arm, which was a confounding factor.
- Conversely, little variation of cost-offsets and QALY gains was observed when comparing DCV+SOF to SOF+RBV, as a result of relatively similar and highly efficacious rates of SVR.

Figure 2: Cost-effectiveness scatterplot (DCV+SOF versus no treatment)

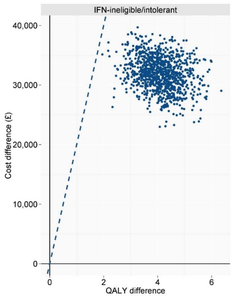
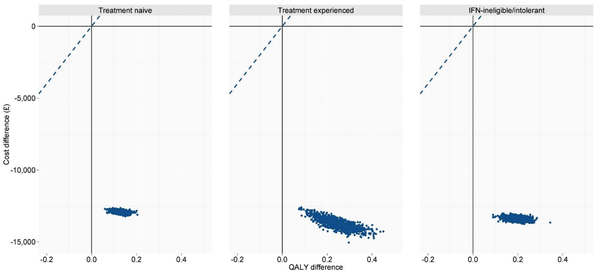


Figure 3: Cost-effectiveness scatterplot (DCV+SOF versus SOF+RBV)



Conclusion

- Historically, HCV genotype 3 patients who were unable to receive interferon had no available treatment option.
- Recent EASL guidelines recommend the combination of DCV+SOF in these patients[27].
- Based upon a willingness-to-pay threshold of £20,000/QALY, 12 weeks of DCV+SOF appears a cost-effective treatment option for patients chronically infected with HCV genotype 3 in all scenarios.
- Further, compared to SOF+RBV, treatment with DCV+SOF results in improved quality of life and reduced total costs, and therefore is likely to represent significant value.

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