Estimating the cost-effectiveness of daclatasvir regimens for patients with advanced chronic hepatitis C in the UK

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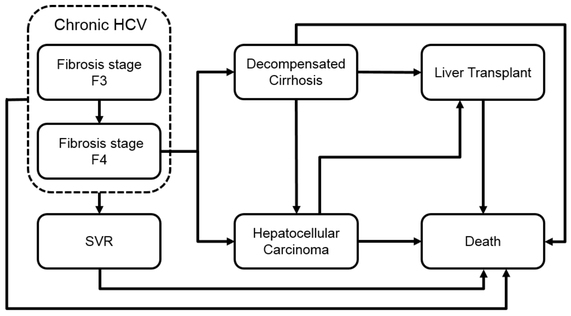
Introduction

- Chronic infection with the hepatitis C virus (HCV) can lead to end-stage liver disease (ESLD) complications including decompensated cirrhosis (DC) and hepatocellular carcinoma (HCC) [1-3], with patients in advanced fibrosis stages being at highest risk.
- The availability of effective treatment for these patients is an area of unmet medical need, with standard of care (SoC) based upon a pegylated interferon-alfa and ribavirin (PR) backbone, which is associated with efficacy and tolerability issues [4, 5].
- Important clinical advances have been made in recent years, with the introduction of direct-acting antivirals (DAAs) that are associated with substantially increased rates of sustained virologic response (SVR), fewer tolerability issues and shorter treatment durations. Daclatasvir is an example of a new generation DAA that has recently been licensed by the European Medicines Agency via accelerated assessment [6].
- The objective of this study was to assess the cost-effectiveness of daclatasvir plus sofosbuvir (DCV+SOF) versus SoC in treatment-naïve patients with HCV genotypes 1, 3 and 4 and advanced disease (METAVIR score ≥F3).

Methods

- A published Markov model [7-10] was used to estimate the relative cost-effectiveness of HCV treatments over a lifetime horizon in a cohort that were 67% male and had a mean age of 50 years [11-13].
- Patients were distributed across METAVIR fibrosis stages F3 and F4 (78.6% and 21.4%, respectively [12]), and progress through fibrosis stages to ESLD complications and death according to published disease state transition rates [14,15] (**Figure 1**).

Figure 1: Model flow diagram



- UK-specific costs [16, 17] and health utility estimates [15, 18-20] were sourced (**Table 1**) .
- An annual discount rate of 3.5% was applied.

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

Transition	Rate (SE)	Disease state	Cost (SE)	Utility (SE)
F3 to F4	0.116	F3	£922 (98)	0.66 (0.031)
F4 to DC	0.039 (0.010)	F4	£1,464 (297)	0.55 (0.054)
F4/DC to HCC	0.014 (0.010)	DC	£11,729 (1,954)	0.45 (0.031)
DC/HCC to LTx	0.030 (0.012)	HCC	£10,452 (2,456)	0.45 (0.031)
DC to death	0.130 (0.010)	LTx (Yr 1)	£47,311 (6,843)	0.45 (0.031)
HCC to death	0.430 (0.030)	LTx (Yr 2+)	£1,781 (457)	0.67 (0.066)
LTx (year 1) to death	0.210 (0.046)	Post-SVR (F3)	£922 (98)*	0.72 (0.048)
LTx (year 2+) to death	0.057 (0.012)	Post-SVR (F4)	£1464 (288)*	0.72 (0.048)

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

- All-cause mortality was applied in line with published UK life tables [21].
- DCV+SOF was compared to telaprevir (TVR) combined with PR and no treatment in HCV genotype 1 patients, and PR and no treatment in HCV genotype 3 and 4 patients.
- Efficacy data was sourced from relevant clinical trials [22-25] (**Table 2**). An SVR of 0 was assumed for no treatment.
- Therapy costs were sourced from MIMS [26].

Table 2: Therapy profiles

Regimen	Genotype	Duration (weeks)	SVR % (SE)	Weekly cost (£)
DCV+SOF	1	12	100 (0)	£4,958.37
	3	24	100 (0)	
	4	12	100 (0)	
TVR+PR	1	TVR: 12 PR: 48	62 (11)	TVR: £1,866.50 PR: £191.35
PR	3	24	49 (6)	£191.35
	4	48	45 (8)	

DCV, daclatasvir; IFN, interferon; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response.

- Therapy-related adverse events and discontinuation were not modelled.
- Cost-effectiveness was assessed through the accumulation of total costs, quality-adjusted life years (QALYs) and life years. Probabilistic sensitivity analysis (PSA) was undertaken to assess parameter uncertainty associated with the analysis.
- An SVR threshold analysis was carried out to assess the lower limit of SVR at which DCV+SOF remains cost-effective.

Results

- In HCV genotype 1, treatment with DCV+SOF resulted in incremental costs of £15,344 and £20,864, and QALY gains of 1.95 and 4.88, compared to TVR+PR and no treatment, respectively. (ICERs of £7,864 and £4,277, respectively)
- In HCV genotype 3, treatment with DCV+SOF resulted in incremental costs of £93,362 and £78,603, and QALY gains of 3.02 and 5.85, compared to PR and no treatment, respectively. (ICERs of £30,871 and £13,442, respectively)
- In HCV genotype 4, treatment with DCV+SOF resulted in incremental costs of £27,029 and £18,701, and QALY gains of 3.07 and 5.36, when comparing to PR and no treatment, respectively. (ICERs of £8,806 and £3,491, respectively)
- Therefore, DCV+SOF is predicted to be cost-effective against all comparators, with the exception of PR in HCV genotype 3, assuming a cost-effectiveness threshold of £20,000/QALY.

Figure 2: Cost-effectiveness plane for HCV genotypes 1, 3 and 4

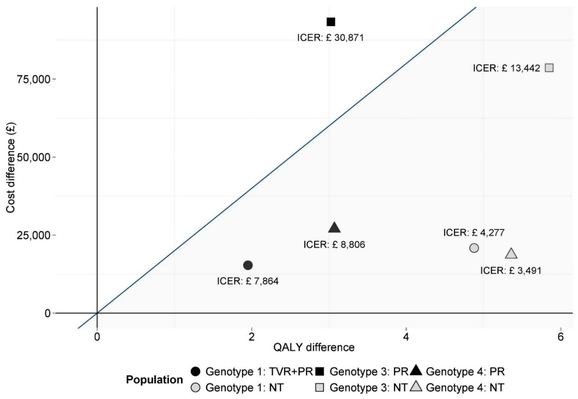
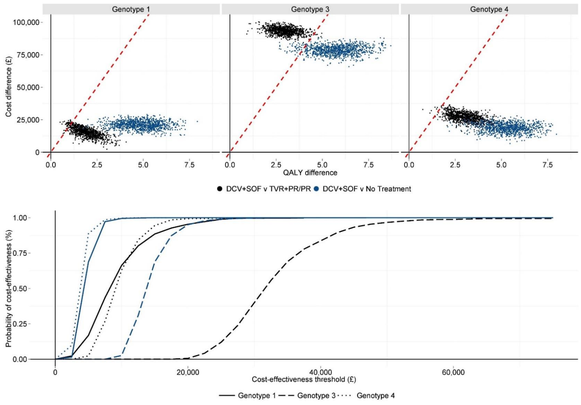


Figure 3: Cost-effectiveness scatterplots and acceptability curves



- Through PSA, results demonstrated that all comparisons, with the exception of DCV+SOF versus PR in genotype 3 patients, have a high likelihood (> 95%) of being cost-effective at the £20,000/QALY threshold (**Figure 3**).
- Increasing the cost-effectiveness threshold to £30,000/QALY resulted in improvements in the likelihood of cost-effectiveness. Predicted probabilities rose to 100% in all comparisons, with the exception of PR in genotype 3 patients, which rose to 40%.
- The largest amount of variability was observed when comparing DCV+SOF to no treatment, due to a larger degree of uncertainty caused by the lack of SVR in patients that are not treated.

Conclusions

- At conventional UK cost effectiveness thresholds, treatment with DCV+SOF is estimated to be cost-effective compared to SoC and no treatment in HCV genotypes 1 and 4. In HCV genotype 3, DCV+SOF is predicted to be cost effective compared to no treatment.
- DCV+SOF has demonstrated high rates of efficacy [22]. This analysis supports the use of DCV+SOF in patients with HCV genotypes 1, 3 and 4 and advanced fibrosis, through demonstration of cost-effectiveness against the majority of comparators.

References

[1] European Association for the Study of the Liver. J Hepatol. 2014;60(2):392-420.
[2] World Health Organization. Guidelines for the screening, care and treatment of persons with hepatitis C infection. 2014. Available from: http://www.who.int/hiv/pub/hepatitis/hepatitis-c-guidelines/en/ [accessed January 2015].
[3] Kanwal F, et al. Gastroenterology. 2010;140(4):1182-8.e1.
[4] Afdhal NH, et al. Clinical Liver Disease. 2012;1(3):63-4.
[5] Kemmer N, et al. Liver International. 2007;27(10):1297-310.
[6] European Medicines Agency. European Medicines Agency recommends approval of Daklinza in chronic hepatitis C. 2014; updated June 2014. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2014/06/WC500169370.pdf.
[7] McEwan P, et al. Applied Health Economics and Health Policy. 2013;11:53-63.
[8] McEwan P, et al. Hepatology. 2013;58(1):54-64.
[9] McEwan P, et al. Value in Health Regional Issues. 2014;3(0):5-11.
[10] McEwan P, et al. PLoS One. 2015 Jan 30;10(1):e0117334.
[11] Public Health England. Hepatitis C in the UK: 2013 report 2013.
[12] Public Health England. Commissioning template for estimating HCV prevalence by DAT and numbers eligible for treatment 2014.
[13] Medical Research Foundation Nottingham University Hospitals NHS Trust. Host and viral factors associated with outcomes of infection with hepatitis C virus (HCV Research UK). 2014.
[14] Thein H, et al. Hepatology. 2008;48(2):418-31.
[15] Shepherd J, et al. Health Technol Assess. 2007;11(11):1-205, iii.
[16] Martin NK, et al. Hepatology. 2012;55(1):49-57.
[17] Personal Social Services Research Unit. Unit costs of Health & Social Care 2013. 2013.
[18] Wright M, et al. Health Technol Assess. 2006;10(21):1-113, iii.
[19] Grieve R, et al. Gut. 2006;55(9):1332-8.
[20] Sutton A, et al. J Viral Hepat. 2008;15(11):797-808.
[21] Office of National Statistics. National Life Tables, 2010-2012: UK reference tables. 2013; updated 14/10/2014.
[22] Sulkowski MS, et al. N Engl J Med. 2014;370(3):211-21.
[23] Shiffman ML, et al. N Engl J Med. 2007;357(2):124-34.
[24] Hezode C, et al. Phase 3 COMMAND-4 Results. IDWeek; 2014 October 07 - 12; Philadelphia, Pennsylvania.
[25] Jacobson IM, et al. N Engl J Med. 2011;364(25):2405-16.
[26] Haymarket Media Group Ltd. Monthly Index of Medical Specialities (MIMS). 2015 [cited February 2015]; Available from: http://www.mims.co.uk/

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