Combining disease transmission and numbers treated in conventional cost-effectiveness analyses of hepatitis C treatment in the UK

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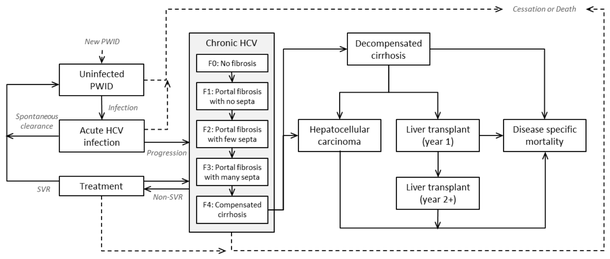
Introduction

- 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].
- The exact prevalence of the condition is not known; however, recent estimates suggest that there are around 214,000 people living with chronic hepatitis C in the UK, with HCV genotypes 1 and 3 predominating [4].
- HCV is unique amongst viruses in that it is curable, with the goal of treatment being the attainment of sustained virologic response (SVR) [2, 5, 6], resulting in the cessation of disease progression in approximately 99% of patients [1, 2].
- The predominant source of infection in the UK is high-risk behaviour among people who inject drugs (PWID) [7]. Latest estimates predict that up to 90% of current HCV infections in the UK are in PWID [7], and 20-68% of PWID in the UK are infected with HCV [8-10]. Reducing the infected population via treatment has been proposed to prevent future infections [9].
- This study evaluated the cost-effectiveness of daclatasvir+sofosbuvir (DCV+SOF) versus telaprevir+pegylated interferon-alfa+ribavirin (TVR+PR) and no treatment, in a cohort of people at high transmission risk and with advanced disease. TVR+PR was selected as the active comparator due to conventional standard of care being protease inhibitor-based triple therapy and the higher market share of TVR versus alternatives.
- Cost-effectiveness estimates that accounted for future infections avoided were contrasted to those obtained from a conventional cost-effectiveness analyses.

Methods

- A previously presented model [11], based on a combination of established HCV disease progression and disease transmission models [12-16], was used **(Figure 1)**.
- The deterministic compartment model simulates susceptible PWID who may become acutely infected with HCV, and consequently either spontaneously clear the infection or progress to chronic hepatitis C.
- The PWID population is stratified by transmission risk (low versus high) and receipt of opiate substitution therapy (OST); PWID who receive OST are suggested to have a more predictable lifestyle and be more easily accessed for receipt of antiviral therapy, decreasing transmission risk.
- If individuals with chronic HCV infection receive treatment, they may achieve SVR, and become susceptible to reinfection, or fail treatment and remain chronically infected. Following treatment failure, re-treatment was not modelled.
- The burden of new infections was estimated based on the simulation of a chronically infected patient modelled from F0, who may progress through liver fibrosis stages, and from stages F3 and F4 to DC, HCC, liver transplant or death.

Figure 1: Model flow diagram



- Dynamic, fibrosis stage-specific, HCV genotype 1 transition rates based on a meta-regression analysis and informed by UK demographic data from the same study were utilised alongside static ESLD disease progression rates [17, 18] **(Table 1)**.
- UK-specific disease state costs and utilities [18-21] **(Table 2)** were utilised and discounted annually at a rate of 3.5%. Where required, costs were inflated to 2013 values using the Hospital & Community Health Services (HCHS) Index [22].

Table 1: Disease state transition rates

Transition	Rate
F0 to F1	0.077
F1 to F2	0.092
F2 to F3	0.145
F3 to F4	0.116
F4 to DC	0.039
F4/DC to HCC	0.014
DC/HCC to LTx	0.030
DC to Death	0.130
HCC to Death	0.430
LTx (Yr 1) to Death	0.210
LTx (Yr 2+) to Death	0.057

DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LTx, liver transplant; SVR, sustained virologic response; Yr, year.

Table 2: Disease state costs and health utility

Disease state	Cost (£)	Utility
F0	188	0.77
F1	188	0.77
F2	975	0.66
F3	975	0.66
F4	1,547	0.55
DC	12,399	0.45
HCC	11,048	0.45
LTx (Year 1)	50,009	0.45
LTx (Year 2+)	1,883	0.67
Post-SVR (F0-F1)	352*	0.82
Post-SVR (F2-F3)	975*	0.72
Post-SVR (F4)	1,547*	0.72

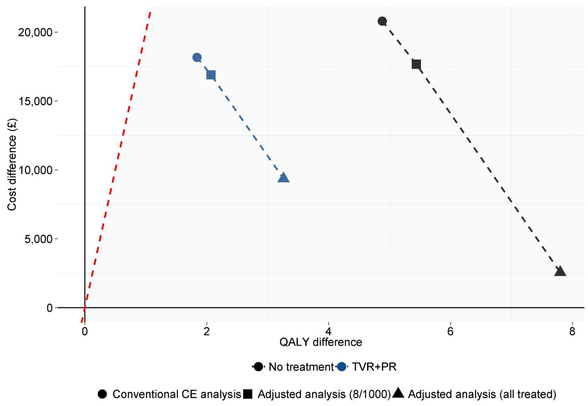
DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LTx, liver transplant; SVR, sustained virologic response.
* Applied in year of treatment only

- Data inputs pertaining to treatment and transmission risk of PWID were sourced [10, 23] and are based upon the PWID population in Edinburgh.
- The size of the total PWID population was assumed to be fixed; the entry rate of new PWID was balanced against the input rates of death and cessation of drug use. The rate of OST recruitment and changes in risk category were balanced against duration of OST and time at high risk, to give constant proportions of PWID at high risk and receiving OST over time. Acute and chronically infected individuals were assumed to be equally infectious.
- Weekly therapy costs of £4,958.39, £1,866.50 and £191.35, for DCV+SOF, TVR and PR, respectively, were sourced from MIMS [24].
- SVRs for patients in F3-F4 (95% and 59% for DCV+SOF and TVR+PR, respectively) were obtained from a matching-adjusted indirect comparison of the two regimens [25], which adjusts for baseline differences between trials.
- Therapy-related disutilities of 0.035 and 0.102, estimated from rates of adverse events observed in pivotal trials [25], were applied to patients undergoing treatment with DCV+SOF and TVR+PR, respectively.
- Treatment discontinuation and adverse events were not modelled.
- In order to quantify the health economic value of HCV treatment unaccounted for in conventional economic analyses, the cost offsets and quality-adjusted life-year (QALY) gains associated with reduced disease transmission in the PWID population were estimated for each treatment regimen.
- Results were accumulated over the period 2015-2065 and presented per patient treated.
- Conventional cost-effectiveness evaluations of DCV+SOF versus TVR+PR and versus no treatment in HCV genotype 1 were also undertaken over a lifetime horizon (80 years), to explore the impact of the potential underestimation of treatment benefit from reduced onward transmission on cost-effectiveness estimates.
- The population evaluated in the conventional analysis were aged 50 years, 67% male and distributed across fibrosis stages F3 and F4 (78.6% and 21.4%, respectively) [4, 25], to fit with European guidelines which recommend prioritisation of treatment in patients ≥ F3 [5].
- Two treatment uptake scenarios were undertaken; an "ideal" scenario, in which all infected PWID were treated immediately; and a more "real-world" scenario, in which a proportion (8/1,000) of PWID were treated annually.

Results

- In the conventional cost-effectiveness analysis, DCV+SOF was associated with incremental per-patient costs of £18,166 and incremental benefits of 1.84 QALYs **(Figure 1)**. The resulting incremental cost-effectiveness ratio (ICER) was £9,867 compared to TVR+PR. Compared to no treatment, DCV+SOF treatment was associated with incremental costs of £20,798 and QALY gains of 4.88; predicted ICER of £4,263.

Figure 2: Cost-effectiveness plane



- When considering the reduced transmission analysis, compared to TVR+PR, additional per-patient discounted cost savings of £8,803 and QALY gains of 1.42 were estimated for DCV+SOF, from 1,845 future infections and 328 related long-term complications avoided over the 2015-2065 period if all patients were treated **(Table 3)**. The associated ICER decreased from £9,867 to £2,869.
- Assuming 8/1,000 PWID were treated, the ICER decreased from £9,867 to £8,156.
- Similarly, additional per-patient discounted cost savings of £18,236 and QALY gains of 2.92 were estimated, from 3,564 future infections and 682 long-term complications avoided, assuming all patients were treated. The associated ICER decreased from £4,263 to £328.
- Assuming 8/1,000 PWID were treated, the ICER decreased from £4,263 to £3,250.

Table 3: Incremental results of disease transmission analysis

Incremental results	DCV+SOF v TVR+PR	DCV+SOF v no treatment
New chronic infections (2015-2065)	-1,845	-3,564
Complications of new chronic infections		
DC	-128	-265
HCC	-54	-111
Liver transplant	-20	-41
Liver related death	-126	-264
Discounted results (2015-2065)		
New chronic infection costs	-£8,803	£18,236
New chronic infection QALY losses	1,42	-2.92

DC, decompensated cirrhosis; DCV, daclatasvir; HCC, hepatocellular carcinoma; PR, pegylated interferon-alfa+ribavirin; QALY, quality-adjusted life years; SOF, sofosbuvir; TVR, telaprevir.

Conclusions

- In addition to the avoidance of future ESLD complications in the treated individual, successful treatment of chronic infection may provide additional benefits through the prevention of future infections in others.
- Although the analysis demonstrated here has been restricted to a specific subpopulation of patients (PWID with HCV genotype 1 and advanced fibrosis), it demonstrates the potential for the significant underestimation of cost-effectiveness when conventional analyses are undertaken.
- The impact of SVR on future disease transmission and consequences of infections avoided should be taken into consideration when evaluating the cost-effectiveness of HCV treatment, especially among groups at high risk of transmission, such as PWID.

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This research was funded by Bristol-Myers Squibb Pharmaceuticals Ltd.

Presented at the 20th annual meeting of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), May 16-20th 2015, Philadelphia, USA.

Bristol-Myers Squibb