Research Article

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Viral Hepatitis

Prioritization of HCV treatment in the direct-acting antiviral era: An economic evaluation

Natasha K. Martin[1,2,*], Peter Vickerman[2], Gregory J. Dore[3], Jason Grebely[3], Alec Miners[4], John Cairns[4], Graham R. Foster[5], Sharon J. Hutchinson[6,7], David J. Goldberg[6,7], Thomas C.S. Martin[8], Mary Ramsay[9], the STOP-HCV Consortium, Matthew Hickman[2]

[1]*Division of Global Public Health, University of California San Diego, San Diego, USA;* [2]*School of Social and Community Medicine, University of Bristol, UK;* [3]*Kirby Institute, UNSW Australia, Sydney, Australia;* [4]*Faculty of Public Health and Policy, London School of Hygiene and Tropical Medicine, UK;* [5]*Queen Mary's University of London, UK;* [6]*Glasgow Caledonian University, UK;* [7]*Health Protection Scotland, UK;* [8]*Guy's and St Thomas's NHS Foundation Trust, London, UK;* [9]*Public Health England, UK*

See Editorial, pages 5–6

Background & Aims: We determined the optimal HCV treatment prioritization strategy for interferon-free (IFN-free) HCV direct-acting antivirals (DAAs) by disease stage and risk status incorporating treatment of people who inject drugs (PWID).

Methods: A dynamic HCV transmission and progression model compared the cost-effectiveness of treating patients early *vs.* delaying until cirrhosis for patients with mild or moderate fibrosis, where PWID chronic HCV prevalence was 20, 40 or 60%. Treatment duration was 12 weeks at £3300/wk, to achieve a 95% sustained viral response and was varied by genotype/stage in alternative scenarios. We estimated long-term health costs (in £UK = €1.3 = $1.5) and outcomes as quality adjusted life-years (QALYs) gained using a £20,000 willingness to pay per QALY threshold. We ranked strategies with net monetary benefit (NMB); negative NMB implies delay treatment.

Results: The most cost-effective group to treat were PWID with moderate fibrosis (mean NMB per early treatment £60,640/£23,968 at 20/40% chronic prevalence, respectively), followed by PWID with mild fibrosis (NMB £59,258 and £19,421, respectively) then ex-PWID/non-PWID with moderate fibrosis (NMB £9,404). Treatment of ex-PWID/non-PWID with mild fibrosis could be delayed (NMB -£3,650). In populations with 60% chronic HCV among PWID it was only cost-effective to prioritize DAAs to ex-PWID/non-PWID with moderate fibrosis. For every one PWID in the 20% chronic HCV setting, 2 new HCV infections were averted. One extra HCV-related death was averted per 13 people with moderate disease treated. Rankings were unchanged with reduced drug costs or varied sustained virological response/duration by genotype/fibrosis stage.

Conclusions: Treating PWID with moderate or mild HCV with IFN-free DAAs is cost-effective compared to delay until cirrhosis, except when chronic HCV prevalence and reinfection risk is very high.

Keywords: Prevention; People who inject drugs; Hepatitis C; Treatment.
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* Corresponding author. Address: University of California San Diego, 9500 Gilman Drive #0507, La Jolla, CA 92093-0507, USA. Tel.: +1 858 822 4802.
E-mail address: Natasha-martin@ucsd.edu (N.K. Martin).

Abbreviations: HCV, hepatitis C virus; PWID, people who inject drugs; PegIFN, pegylated interferon; RBV, ribavirin; IFN-free, interferon-free; DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; QALY, quality adjusted life-year; NMB, net monetary benefit; ESLD, end stage liver disease; WTP, willingness to pay.

Introduction

Chronic infection with hepatitis C virus (HCV) is a leading cause of morbidity and mortality across the world. Globally, an estimated 80–150 million people are chronically infected with HCV, which if left untreated can lead to cirrhosis, liver cancer, and death [1,2]. In high-income countries, people who inject drugs (PWID) are the main risk group for HCV transmission, contributing to >90% of new infections in settings such as the UK [3].

Effective antiviral treatments for HCV can result in a sustained virological response (SVR, equating to a cure) in the large majority of people [4]. HCV antiviral treatment could also be a key component in preventing HCV transmission through the reduction of chronic HCV prevalence among PWID [5–7]. Previous research has indicated that treating PWID with interferon (IFN)-containing therapy (i.e., pegylated interferon (PegIFN) and ribavirin (RBV)) is likely to be more cost-effective than treating non- or former-PWID with no ongoing risk behavior due to the substantial potential prevention benefit [8]. Current HCV treatment rates in many countries, however, are insufficient to reduce either the rise in end stage liver disease (ESLD) [9,10] or HCV transmission [11].

The HCV antiviral treatment landscape is rapidly changing. SVR rates with new IFN-free direct-acting antivirals (DAAs) are higher than for PegIFN + RBV: at >90% for all genotypes compared

Research Article

to <50% for genotype 1 and up to 80% for genotype 3 [4]. Crucially, IFN-free DAA treatment has improved SVR in people with genotype 1 cirrhosis from ~30% to >80% [12,13]. IFN-free DAAs are highly tolerable, oral-only, shorter duration (12–24 weeks) and will likely involve once daily regimens. These new therapies are associated, however, with considerable treatment costs (e.g., $60,000–80,000 per 12 week course).

Although some new DAA agents have been deemed cost-effective in the UK [14] and are reimbursable in the US and Australia, there is heated debate as to how best to prioritize patients for treatment [15,16]. International guidelines in 2014 suggest prioritizing IFN-free DAA therapy for patients with advanced liver disease [17,18]. A recent analysis from the United States demonstrated that IFN-free DAA treatment among people with mild stages of fibrosis (F0 or F1) is not cost-effective compared to delaying treatment until more moderate stages of fibrosis (F2) [19]. However, these recommendations are based on expected individual patient-level benefit in reduced progression to ESLD, and neglect potential prevention benefits to the population due to the impact on HCV transmission [16].

We therefore use a dynamic model of HCV transmission among PWID, combined with data on disease progression, and treatment to determine the more cost-effective strategy for prioritizing HCV antiviral treatment after diagnosis.

Methods

Mathematical model

An existing dynamic cost-effectiveness model of HCV transmission, disease progression, and treatment was adapted [8] (Supplementary Fig. 1). The model incorporated HCV transmission among PWID, such that HCV infection and reinfection was related to the background prevalence of chronic infection among PWID, which could change over time. The model included the risk of reinfection after treatment for PWID, and also the population benefits of reducing onward transmission. We used the model to examine three chronic HCV prevalence settings among PWID (20%, 40% and 60%) at baseline. This corresponded to baseline incidences of infection/reinfection among PWID of 4% (2.5–97.5% Confidence Interval (95% CI) 3–5%), 9% (95% CI 7–13%), and 21% (95% CI 15–30%), in the 20%, 40%, and 60% chronic prevalence scenarios, respectively. The model was open, with PWIDs entering the population on initiation of injecting and were tracked after permanent cessation of injecting when they were assumed to be no longer at risk of reinfection or transmission.

The model was a deterministic, compartmental model which was stratified by risk status (PWID, former-PWID), HCV genotype (genotype 1 and 4, genotype 2, and genotype 3) and infection status and disease stage (never infected or infected and spontaneously cleared, mild HCV, moderate HCV, compensated cirrhosis [CC], decompensated cirrhosis [DC], hepatocellular carcinoma [HCC], liver transplant, post-transplant). For simplicity, we assumed an individual had one dominant genotype strain which affected treatment SVR, and that an individual's risk of acquiring a specific genotype was related to the circulating prevalence of each genotype. Additionally, for those stages eligible for antiviral treatment (mild HCV, moderate HCV, and compensated cirrhosis), the model was further stratified by treatment status (never treated, on treatment, SVR, non-SVR). Those who achieved SVR were at risk of reinfection; we assumed no change in risk behavior after treatment, so each individual's risk of reinfection was equal to that of primary infection. We assumed that those with mild or moderate fibrosis who achieved SVR were at no risk of further liver disease progression unless they were reinfected. Based on clinical evidence, we assumed that those with compensated cirrhosis who achieved SVR remained at elevated risk of disease progression due to existing liver damage [20,21]. Individuals who did not attain SVR proceeded through the natural history of liver disease progression and were assumed to be ineligible for retreatment, as no drugs are currently licensed for retreatment of IFN-free DAA failures. The base-case assumed the risk of transmission or acquisition of HCV was independent of disease stage or duration of injecting, as evidence is unclear whether, apart from the first year, injecting risk increases or decreases over the course of an injecting career.

Antiviral treatment scenarios

We explored three antiviral treatment scenarios to assess whether differences in the characteristics of the treatment course affected the prioritization strategy.

1. Future IFN-free DAA scenario: IFN-free DAAs for 12 weeks with 95% SVR for all disease stages and genotypes [4,22–24]. We used this scenario as the base-case for most of our analyses.
2. 'Current' DAA scenario: IFN-free DAAs with 90–95% SVR for mild/moderate HCV, and 70–90% SVR for compensated cirrhosis depending on genotype. Treatment durations are 8–12 weeks (genotypes 1 and 2) and 24 weeks (genotype 3).
3. 'Current' DAA scenario except PegIFN/RBV for mild G3: As in scenario (2) but with PegIFN/RBV for mild genotype 3.

Assumptions regarding SVR and treatment durations, and costs for different HCV antiviral treatment regimes can be found in Table 1. As future costs of many IFN-free regimens are not yet determined, we assumed a weekly drug cost of £3300 per week (cost of sofosbuvir + ledipasvir [25]). Treatment delivery costs assumed are £90 per week [26] for ex/non-PWID, PWID delivery is 120% of non/ex-PWID cost [8]. Treatment delivery costs included the costs of staff time and tests/investigations; we assumed higher treatment delivery costs for PWID due to additional staff time and psychiatric assessments as in previous economic evaluations [8,27,28]. In the sensitivity analysis, we varied the SVR by disease stage and genotype, cost, and treatment duration.

Prioritization analysis using cost-effectiveness methods

For each level of chronic HCV prevalence in PWID (20%, 40% and 60%), we compared the following treatment options to assess the most cost-effective prioritization strategy:

Baseline

Treat everyone with compensated cirrhosis (mainly ex-PWID with no ongoing risk so have very little 'treatment as prevention' benefit) every year. We chose this baseline to represent current guidance and the real-world prioritization of treating individuals with advanced disease (CC) first. We did not treat individuals with DC, HCC, or post-transplant, as treatment for these groups is recommended on a case-by-case basis and disease progression outcomes are still uncertain; individuals who are not in these stages at baseline were all treated at the CC stage upon progression.

Intervention

In addition to baseline treatment of all those with CC, we modeled treating, in addition, each year for the next 10 years:

- 1 PWID (in our population of 1000 PWID) at the mild stage
- 1 PWID (in our population of 1000 PWID) at the moderate stage
- 1 non or ex injector at the mild stage
- 1 non or ex injector at the moderate stage

As shown in previous work including population-level treatment as prevention benefits [8,27], the cost-effectiveness of treatment was strongly dependent on the treatment rate. The higher the treatment rate for PWID, the greater the prevention benefits, and therefore the greater the cost-effectiveness of treatment for PWID. Therefore, we conservatively examined a very low treatment rate among PWID because HCV treatment rates among PWID are extremely low in the UK and most other global settings (<1% PWID per year) and so it does not overly bias towards treatment of PWID.

We calculated the costs and quality adjusted life-years (QALYs) for a further 40 years, giving a total time horizon of 50 years.

The cost-effectiveness analysis used a UK health care provider perspective. Costs were valued in 2014 UK pounds (£1 = €1.3 = $1.50 USD) and health outcomes were expressed in QALYs. Both costs and health utilities were discounted at 3.5% per annum in the base-case according to UK National Institute for Health and Care Excellence (NICE) guidelines [29].

Uncertainty in the underlying parameters was accounted for, such that epidemiological parameters, disease transition probabilities, costs, and health benefits were analysed using multivariate random sampling from appropriate distributions. For each of the 1,000 sampled parameter sets, we simulated three chronic HCV baseline prevalence scenarios among PWID at equilibrium, which represented the range of prevalence observed across most sites in Europe and other