A Systematic Review of Economic Evidence in Hepatitis C: an Overview of Cost, Utility, and Cost-effectiveness Data

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BACKGROUND

- Chronic infection with hepatitis C virus (HCV) is a major cause of liver disease, which may lead to cirrhosis and predispose patients to the development of liver cancer.[1]
- Approximately 159 to 185 million individuals (2.4%–2.8% of world population) are infected with HCV.[2,3]
  - In Western Europe, HCV prevalence is estimated at 2.4%, ranging from 0.4% in Germany to 5.2% in Italy.[2,4]
  - Prevalence is believed to be higher in Eastern Europe,[5] the Middle East,[5] and China.[2]
- Six HCV genotypes, numbered 1 through 6, and many subtypes have been described.[6] Genotype 1 (subtypes 1a and 1b) is the most prevalent genotype worldwide.
- Chronic infection can be associated with variable degrees of hepatic inflammation and fibrosis progression, regardless of HCV genotype and viral load. Between 10% and 40% of patients with chronic HCV infection develop cirrhosis, depending on the presence of other cofactors.[7]
- The approved and well-accepted standard of care for chronic HCV is the combination of pegylated interferon (PEG-IFN) alfa and ribavirin.[8]
- Many drugs for HCV are at various stages of preclinical and clinical development. New therapeutic strategies aim toward treating specific genotypes, increasing efficacy, shortening treatment, simplifying dosing regimens, treating without interferon, and improving tolerability and patient adherence.

OBJECTIVE

- To perform a systematic literature review of economic evidence for genotype 1 HCV treatments to identify all published economic evaluations of treatments and studies reporting health-state utility weights, resource use, and direct and indirect cost estimates.

METHODS

Study Identification

- A systematic review of the following databases was performed per a prespecified, clearly defined protocol from 01 January 2000 to 12 November 2012 (without limitations on publication language): Medline, Medline In-Process, EconLit, Embase, BIOSIS, and the Cochrane Library.
- Search terms comprised combinations of free-text and medical subject heading (MeSH) terms:
  - Health condition of interest (disease) (e.g. "Hepatitis C, Chronic" [MeSH])
  - Study type of interest: economic evaluations (e.g. "Costs and Cost Analysis" [MeSH], "Cost-Benefit Analysis" [MeSH], "Economics, pharmaceutical" [MeSH])
  - Interventions of interest: terms for PEG-IFN alfa-2a, PEG-IFN alfa-2b, PEG-IFN alfa, ribavirin, telaprevir, boceprevir, simeprevir, daclatasvir, asunaprevir, faldaprevir, BI 207127, sofosbuvir, BMS-791325, BMS-986094, ledipasvir (GS-5855), GS 9451, tegobuvir, ABT-450/r, ABT-333, ABT-267, and ABT-072
- Relevant conference proceedings, Internet resources, health technology assessment (HTA) websites, and bibliographic reference lists of identified systematic reviews and meta-analyses were searched.

Study Selection

- The criteria for screening of the articles was as follows:
  - Population: patients with genotype 1 HCV, with or without concomitant liver diseases
  - Interventions of interest (applied to economic evaluations only): interferon-free and interferon-containing regimens, including combinations of the treatments listed above
  - Study types of interest: economic evaluations, studies reporting utility weight estimates, and studies reporting costs and resource-use estimates
  - Exclusionary terms: irrelevant publication types, including nonsystematic reviews, comments, editorials, letters, case reports, or studies in animals but not humans
- One researcher reviewed titles and abstracts for potential relevance (Level 1 screen) and reviewed the potentially relevant full-text articles (Level 2 screen). A second researcher resolved any uncertainty about study inclusion, checked a random selection (5%) of identified titles and abstracts and full-text articles, and confirmed eligibility of all studies selected after the Level 2 screen.
- For each eligible study, one researcher extracted the data of interest, while another researcher verified the data with the original sources.

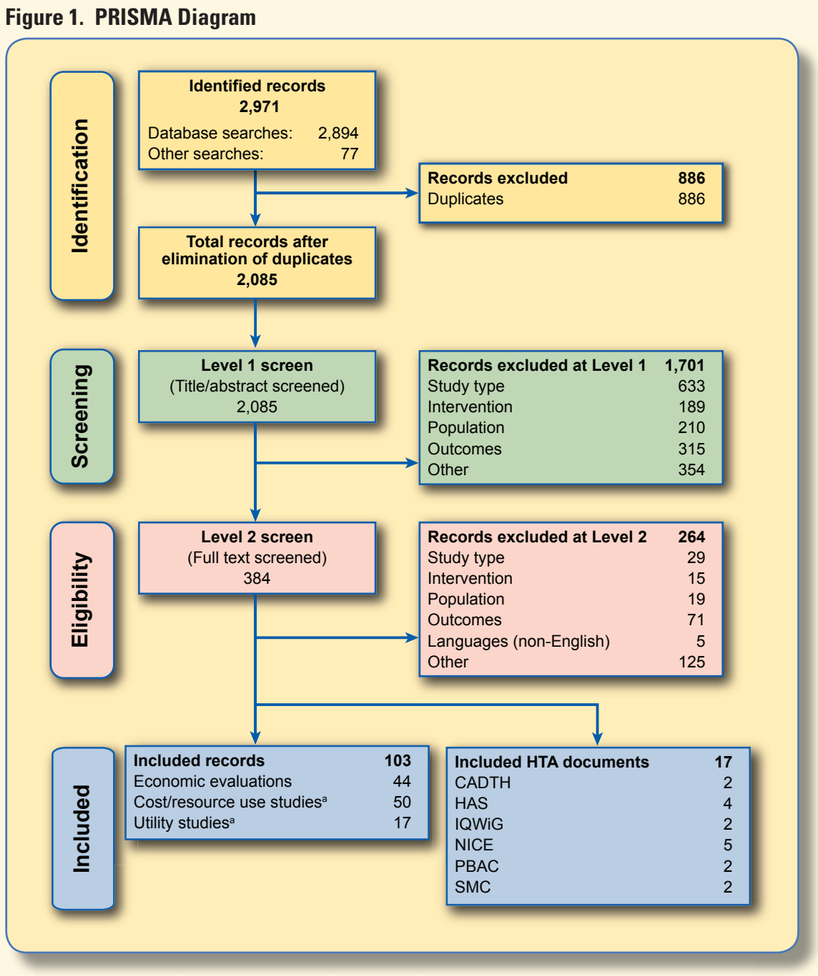
Quality Assessment

- All included economic evaluations were assessed using the quality criteria presented in the National Institute for Health and Care Excellence (NICE) single technology appraisal template.[9]

RESULTS

- Figure 1 shows the results of the systematic literature review.

Figure 1. PRISMA Diagram



PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Source: Adapted from Moher et al., 2009.[10]

[a] Some cost/resource use studies also reported utility data and vice versa. Therefore, some studies were included in both of these categories.

- Table 1 presents the range of reported annual direct and indirect costs and utilities for important and commonly reported health states in HCV.

Table 1. Costs and Utilities for Different Health States in HCV From Primary Studies

Health State	Range of Direct Costs[a]	Range of Indirect Costs[a]	Range of Utilities
All HCV	$11,792.52-$50,906.50[b]	($1,571.45–only the cost of absence from work) $3,491.17-$10,838.08	0.63-0.87
HCV without liver disease	$11,573.51-$17,902.38[b]	Not available[d]	Not available[d]
Compensated cirrhosis	$17,650.23-$23,581.47[b]	$5,485.79[c]	0.56-0.84
Decompensated cirrhosis	$43,997.40[c]	$6,036.97[c]	0.55-0.76
Hepatocellular carcinoma	$61,491.09[b,c]	Not available[d]	Not available[d]
Liver transplant	$118,840.69[b,c]	$12,828.35[c]	Not available[d]
Liver transplant after 1 year	$57,662.67[c]	Not available[d]	Not available[d]
End-stage liver disease	$45,814.96-$64,007.30	Not available[d]	Not available[d]
Patients in SVR	$9,494.93 (HCV related)[c]	Not available[d]	0.787-0.90

[a] Unless noted otherwise, costs are all-cause costs and are reported in 2012 US dollars. Costs reported in different currencies were converted to US dollars using the relevant year's Purchasing Price Parities (PPP) and inflated to 2012 prices using the Consumer Price Index (CPI) levels of inflation (original cost/PPP x CPI).

[b] One additional study reported lower costs, but it was not clear whether these were HCV-related costs or all-cause costs.

[c] Reported in only one study.

[d] These data were not available in the identified primary cost and utility studies identified within this systematic review.

- Many health states did not have cost or utility data available in the recently published material. In the economic evaluations, these data were usually taken from previous models or older primary sources.
- Most of the cost studies reported overall direct costs for all patients with HCV, ranging from $11,792.52 to $50,906.50 per-patient per-year.
- The liver transplant disease state had the highest potential all-cause annual direct costs, up to $118,840.69 per-patient, and the HCV without liver disease health state had the lowest, up to $11,792.52 per-patient per-year.
- Indirect costs were not frequently reported, but they were also highest in the liver transplant population, with an estimated cost of $12,828.35 per-patient per-year.
- For the disease states presented, utilities were reported only for patients with compensated cirrhosis, decompensated cirrhosis, patients achieving a sustained virological response (SVR), or for all patients with HCV. Predictably, utilities were lowest for patients with decompensated cirrhosis (the worst disease state) and highest for patients in SVR (the best disease state).
- Utilities were as low as 0.40 for treatment-experienced patients with compensated cirrhosis. However, this review did not identify utility data for some of the more severe disease states.
- Table 2 presents the annual health care resource use for patients with HCV.

Table 2. Annual Health Care Resource Use for Patients With HCV

Resource	Range of the Number of Annual Visits Per Patient With HCV
Emergency room visit	0.38-0.76
Hospitalisation	0.30-3.94
Physician visit	7.71-19.48

- In cost-effectiveness analyses, boceprevir triple therapy had the lowest range limit for treatment-naïve and treatment-experienced patients (i.e., potential to have the lowest ICER: $9,956.21 for treatment-naïve patients; $4,580.01 for treatment-experienced patients).
- Boceprevir also had the highest range limit for treatment-naïve and treatment-experienced patients (i.e., potential to have the highest ICER: $41,743.85 for treatment-naïve patients; $35,085.09 for treatment-experienced patients).
- The range of ICERs all supported the notion that both treatments are below the established cost-effectiveness threshold of £20,000 per quality-adjusted life-year. This was the conclusion reached by NICE, which recently approved both therapies for treatment of patients with HCV.

Table 3. Cost-effectiveness: ICERs for Different Treatment Strategies

Population	Range of ICERs[a]
Treatment naïve	
Boceprevir triple therapy vs PEG-IFN + ribavirin	$9,956.21-$41,743.85
Telaprevir triple therapy vs PEG-IFN + ribavirin	$14,183.22-$27,573.16
Treatment experienced	
Boceprevir triple therapy vs PEG-IFN + ribavirin	$4,580.01-$35,085.09
Telaprevir triple therapy vs PEG-IFN + ribavirin	$14,862.91-$28,891.75

[a] All costs are reported in 2012 US dollars. ICERs reported in different currencies were converted to US dollars using 2010 PPP and inflated to 2012 prices using the CPI levels of inflation (original cost/PPP x CPI).

DISCUSSION

- There are a number of gaps in the cost and utility data for all of the relevant disease states, which makes it difficult to make any firm conclusions and to adapt or develop models in different settings.
- Treatment-experienced patients are more difficult to treat than treatment-naïve patients. However, as they have already failed treatment with PEG-IFN plus ribavirin, the triple therapy options may appear comparatively more cost-effective.
- A wide range of cost-effectiveness outcomes were found for boceprevir triple therapy and telaprevir triple therapy when compared with PEG-IFN plus ribavirin alone. This wide range suggests that there may be other drivers in the treatment-naïve and treatment-experienced groups that could be influencing the ICERs for these interventions.
- Recent economic models tended to use utility data and/or cost and resource use data from previous models or HTA submissions, and they generally adhered to previous HCV model structures. They have not evolved with the knowledge of HCV. There is a particular scarcity of up-to-date country-specific utility data.
- The relative efficacy differences between upcoming treatment alternatives may be quite small, which may present challenges in cost-effectiveness analysis.
- Due to high variance in the SVR rates achieved with PEG-IFN and ribavirin alone, it might become challenging to accurately estimate the efficacy gain of adding a direct acting antiviral. Indirect inter-trial comparisons also might be affected. Marginal efficacy gains may become smaller, and the ICERs could potentially seem very large when conducting incremental analysis between the newer agents.
- There will be limited head-to-head data for upcoming treatment options; therefore, the models will need to incorporate data from a number of indirect comparisons and network meta-analyses.
- Determining the cost-effectiveness of varying treatment strategies and sequences may become a much more pressing issue when multiple treatment alternatives become available.

CONCLUSIONS

- The systematic literature review identified 44 economic evaluations, 17 HTA documents, 50 cost/resource use studies, and 17 utility studies.
- HCV has potentially large annual costs per patient, up to $118,840.69 for patients requiring liver transplant, as well as a large impact on quality of life, with utilities as low as 0.55 for all patients with HCV with decompensated cirrhosis and 0.40 for treatment-experienced patients with compensated cirrhosis. Utilities are likely to be even lower for the more severe disease states; however, this was not reported in the available data.
- In light of upcoming treatment alternatives, model refinement may be necessary to capture the increasingly complex treatment decisions that will be required. Enhanced utility and cost studies and more advanced modeling techniques may be needed.

REFERENCES

Please see handout for complete reference list.

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Presented at: ISPOR 16th Annual European Congress
November 2-6, 2013
Dublin, Ireland