A Systematic Review of Economic Evidence in Hepatitis C: Methods Used in Recent Economic Evaluations

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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]
- Six main HCV genotypes, numbered 1 through 6, and many subtypes have been described.[2] Genotype 1 (subtypes 1a and 1b) is the most prevalent genotype worldwide.
- The approved and well-accepted standard of care for chronic HCV is the combination of pegylated interferon (PEG-IFN) alfa and ribavirin.[3]
- Recently, telaprevir and boceprevir were approved for use in combination therapy with PEG-IFN alfa and ribavirin for treating patients with genotype 1 HCV.
- 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 evaluations in genotype 1 HCV treatments and to summarise and assess the methods used in these evaluations.

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 any identified systematic reviews and meta-analyses were searched.

Study Selection

- The criteria for screening of the articles were 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 type of interest: economic evaluations
  - 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.

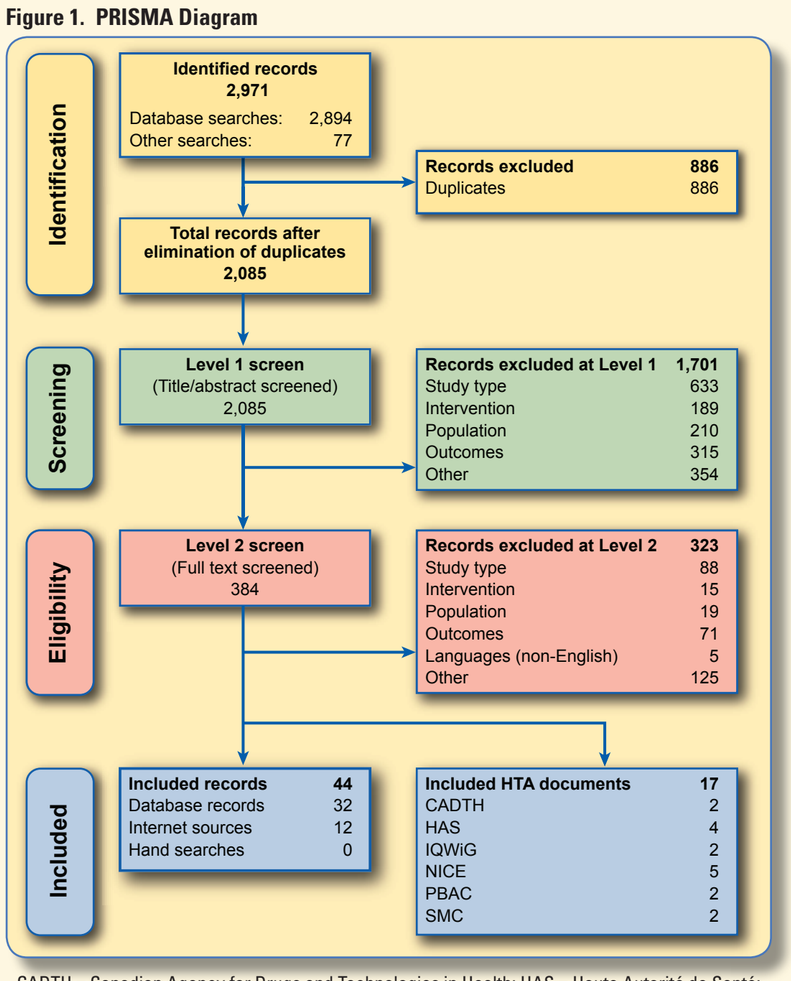
Quality Assessment

- 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.[4]

RESULTS

- Figure 1 shows the results of the systematic review.
- Most models (n = 24) used a Markov structure; decision-analytic models were also common (n = 10) (Figure 2).
- Most models (n = 28) used a lifetime horizon. All models used long-term time horizons, with the smallest time horizon being 20 years.
- Many publications did not report the time horizon used in their models (n = 14) or the model structure (n = 7).
- Most analyses were performed in the United States (n = 13), the UK (England, Wales, and Scotland) (n = 13), and Germany (n = 7) (Figure 3).
- Although this literature search was designed to identify data on any of the new interferon-free regimens, all of the included economic evaluations were for the existing interferon-containing regimens (including more recently approved treatment combinations).

Figure 1. PRISMA Diagram



CADTH = Canadian Agency for Drugs and Technologies in Health; HAS = Haute Autorité de Santé; IQWiG = Institute for Quality and Efficiency in Healthcare; PBAC = Pharmaceutical Benefits Advisory Committee; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SMC = Scottish Medicines Consortium.

Source: Adapted from Moher et al., 2009.[5]

Figure 2. Model Structures Used in the Included Economic Evaluations

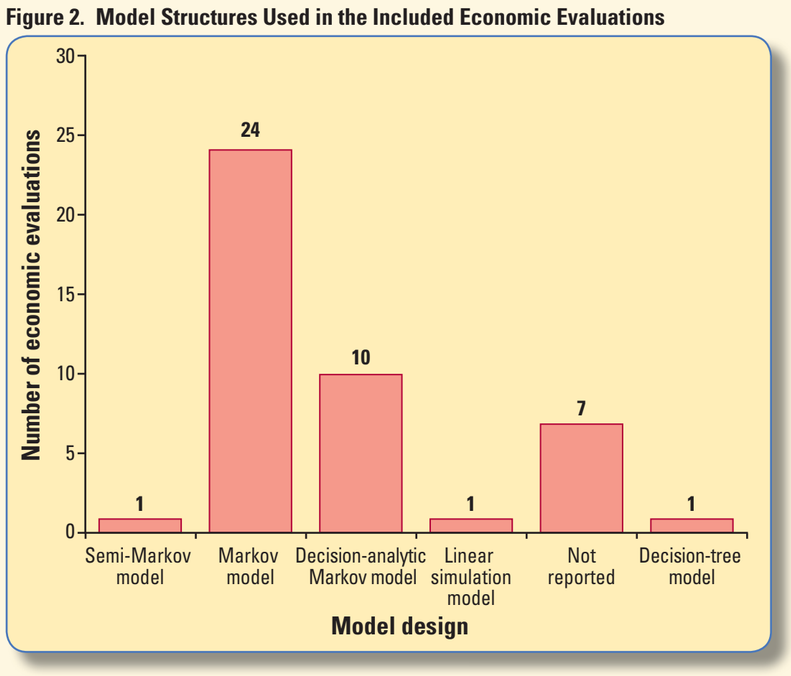
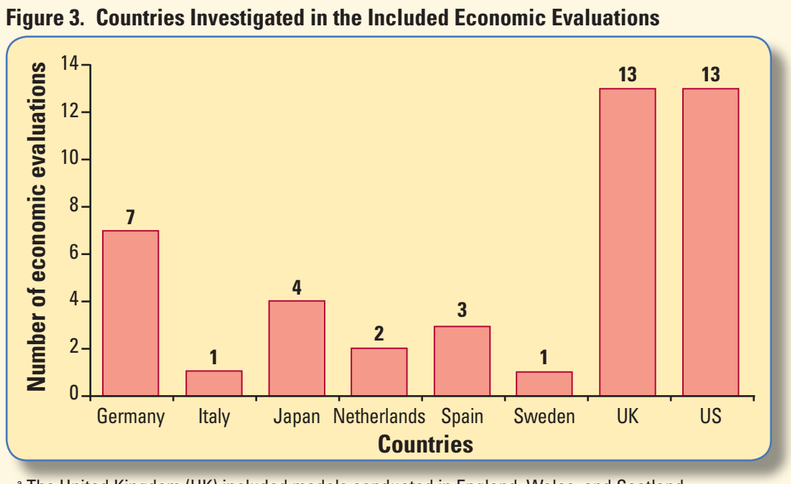


Figure 3. Countries Investigated in the Included Economic Evaluations



[a] The United Kingdom (UK) included models conducted in England, Wales, and Scotland.

- The most common comparisons were between the newer treatments of boceprevir triple therapy with PEG-IFN and ribavirin alone (n = 8) and telaprevir triple therapy with PEG-IFN and ribavirin alone (n = 11) (Table 1).
- The other models were mainly comparisons of PEG-IFN plus ribavirin: different PEG-IFNs (PEG-IFN alfa-2a versus PEG-IFN alfa-2b), different modes of treatment, or different treatment schedules.
- Two recent NICE submissions were included: telaprevir triple therapy (with PEG-IFN plus ribavirin) and boceprevir triple therapy. They used different models; however, their structures and some inputs were based on previous appraisals for PEG-IFN plus ribavirin.

DISCUSSION

- The following limitations in the included economic evaluations may have affected the cost-effectiveness outcomes:
  - Many models were based on previous iterations of economic models or previous HTA submissions, including model structures and/or inputs.
  - The models may not have adequately captured all health benefits and costs in their quality-adjusted life-year calculations (e.g., drug wastage costs).
  - Many models did not consider response-guided therapy, which may impact costs of treatment by shortening treatment duration for patients who achieve an early response or who do not respond to treatment.

Table 1. Treatment Comparisons Made in Economic Evaluations

Treatment Comparisons Made	Number of Models
PEG-IFN alfa + ribavirin vs. boceprevir triple therapy vs. telaprevir triple therapy	4
PEG-IFN alfa + ribavirin[a]	6
PEG-IFN alfa-2a vs. PEG-IFN alfa-2b	2
Boceprevir triple therapy vs. telaprevir triple therapy	2
PEG-IFN alfa-2a + ribavirin (PEG-IFN alfa-2a monotherapy for patients who cannot have ribavirin)	1
Interferon + ribavirin vs. PEG-IFN + ribavirin	1
Early PEG-IFN/interferon vs. delayed PEG-IFN/interferon + ribavirin	1
PEG-IFN + ribavirin vs. no treatment	5
PEG-IFN alfa-2b + ribavirin vs. interferon alfa-2b + ribavirin vs. no treatment	1
Boceprevir triple therapy vs. PEG-IFN + ribavirin	8
Telaprevir triple therapy vs. PEG-IFN + ribavirin vs. no treatment	2
Telaprevir triple therapy vs. PEG-IFN + ribavirin	11

[a] Includes models comparing different modes or schedules of treatment with PEG-IFN alfa + ribavirin.

  - The models did not account for the possibility of benefits caused by reduced transmission of HCV or the potential costs of HCV reinfection. Doing so would require much longer-term data that may be difficult to accurately incorporate in a model.
  - The models did not incorporate patient factors, such as alcohol consumption or duration of infection, which may have an influence on disease progression.
  - The modelling of subgroups may have been insufficient to accurately capture the incremental costs and benefits within treatment groups.
  - As understanding of HCV grows, so does the knowledge of patient and genetic factors that may influence disease progression or may be important in predicting a patient's response to treatment. These factors were not taken into account in previous models or studies and therefore may be difficult to incorporate in the economic models.
  - Incorporating more detailed patient factors and patient subgroups in the economic models should give a more accurate estimate of cost-effectiveness.
- The recent NICE submissions provided additional detail and related criticism on the submitted models:
  - The telaprevir submission made generalisations for the compensated cirrhosis population that were not comparable with the UK population:
    - The number of people classified as having cirrhosis may not have been sufficient to reflect the higher proportion of patients in the UK with cirrhosis.
    - It is uncertain what effect the larger cirrhosis population in the UK would have on the incremental cost-effectiveness ratios (ICERs). This could decrease the ICER, because patients are at greater risk for poor outcomes, or increase the ICER, because patients with cirrhosis tend to respond less well to treatment.
  - The telaprevir submission unintentionally allowed transition probabilities to vary with age rather than being fixed to age at the time of treatment.
  - Trials used in the boceprevir submission used different definitions of early responders and stopping rules for treatment-naïve and treatment-experienced patients than those in the label.
  - The methods for deriving efficacy estimates in the boceprevir submission were not clearly described.

CONCLUSIONS

- The systematic literature review identified 44 economic evaluations and 17 HTA documents.
- The majority of economic evaluations were of interferon-containing regimens; were performed using lifetime horizon Markov models; and were performed in the United States, the UK, or Germany.
- There are numerous recent economic models; however, these have generally adhered to previous iterations of HCV models or models used in previous HTA submissions and have not evolved with our knowledge of the disease.
- 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 approaches may be needed.

REFERENCES

Please see handout for complete reference list.

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