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Structural Frameworks and Key Model Parameters in Cost-Effectiveness Analyses for Current and Future Treatments of Chronic Hepatitis C

Rebecca Townsend, BSc[1,], Phil McEwan, PhD[1], Ray Kim, MD[2], Yong Yuan, PhD[3]*

[1]*Cardiff Research Consortium, Cardiff, Wales, UK;* [2]*Mayo Clinic College of Medicine, Rochester, MN, USA;* [3]*Bristol-Myers Squibb, Plainsboro, NJ, USA*

ABSTRACT

Objectives: Published economic evaluations have reported available treatments for chronic hepatitis C to be cost-effective as part of the current approach to disease management, but as standards of care evolve, their approach to modeling should be reconsidered. This study aimed to review structural frameworks and key model parameters as reported in current economic evaluations for treatments for chronic hepatitis C, and model the impact of variability across parameters on results. **Methods:** A systematic review of studies published from 2000 to 2011 was performed. Studies were retrieved from five electronic databases using relevant search strategies. Model structures, disease progression rates, utilities, and costs were extracted from included studies, and were qualitatively reviewed and incorporated into a cost-utility model. **Results:** Thirty-four studies were appropriate for data extraction. A common pathway of six disease states was identified. In some studies the early disease stages and/or the decompensated cirrhosis state were further subdivided. Large variability in values used for disease progression rates, utilities, and costs were identified. When incorporated into a model, incremental cost-effectiveness ratios (ICERs) varied: in the least favorable scenario, peginterferon plus ribavirin was dominated by interferon plus ribavirin; and in the most favorable scenario, peginterferon plus ribavirin dominated interferon plus ribavirin ($8,544 per quality-adjusted life year [QALY]; costs are given in 2008 US dollar amounts). Using mean values the ICER was $15,198 per QALY. **Conclusions:** Current models use a simplistic structure resulting from the lack of available data reflecting patient heterogeneity. Key model parameters are currently based on a small number of studies and the variability across these values can affect the interpretation of results.

Keywords: decision making, economic evaluation, health economics methods, hepatitis c, modeling.

Introduction

Chronic hepatitis C is a major cause of progressive liver disease and represents a significant and increasing burden in terms of morbidity, mortality, and costs in both developed and developing countries [1,2]. Factors such as prevalence, cumulative time of exposure to the hepatitis C virus (HCV), and genetic and environmental aspects mean that the disease burden differs across geographic regions. For example, the average time elapsed since exposure in Japan, Italy, and Spain means that a high proportion of patients have already progressed to chronic hepatitis, cirrhosis and, occasionally, hepatocellular carcinoma (HCC); while in the US, the prevalence of the complications of disease progression associated with HCV, such as HCC, are predicted to increase over the next 20 to 30 years as the average time since exposure increases [3].

Chronic hepatitis C is unique among chronic viral infections in that it is considered to be curable, and thus effective treatment, in terms of sustained virological response (SVR), has substantial long-term benefits. In many countries, combination antiviral therapy with peginterferon alfa plus ribavirin has become the standard of care [4,5] and is considered cost-effective over a patient's lifetime for patients with chronic hepatitis C achieving SVRs of 40% in those with genotype 1 HCV, and 75% in those with genotype 2 and 3 [6]. A recent review of cost-effectiveness analyses reported that the majority of published incremental cost-effectiveness ratios (ICERs) fall within published acceptability thresholds [7].

The approach to disease management and treatment continues to evolve, as means of addressing the current and substantial unmet medical needs in hepatitis C are sought. Indeed, the introduction of the first direct-acting antiviral (DAA) therapy is anticipated in 2011. Also, research now indicates that certain biomarkers and differential responses to treatment at earlier periods of measurement (e.g., rapid viral response at 4 weeks) may also influence long-term treatment success across this heterogeneous patient group [8–12]. As treatment benefits are maximized in those who respond, and exposure to adverse events and treatment costs are minimized in those who do not respond, so it can be expected that cost-effectiveness will be maintained or improved.

To assess the true value of current and future standards of care, the relevant benefits and costs must be considered over the lifetime of the patient using appropriate modeling techniques. To ensure that models are fit-for-purpose and that their interpretation by payers and society is accurate and appropriate, it is essential that the design, methodological assumptions, and data input parameters are relevant to the research question posed. To date, no one has reviewed the current model frameworks or underlying data used by published economic evaluations to assess the variability across analyses or quantify its affect on results. In anticipation of the

* *Address correspondence to*: Rebecca Townsend, Cardiff Research Consortium, Eastgate House, 35-43 Newport Road, Cardiff CF24 0AB, UK.
E-mail: rebecca.townsend@capita.co.uk.

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advent of new approaches to treatment and new agents, it is timely to review the currently available analyses and describe their underlying data sources to aid future modeling activities.

The objective of this study is to review the model structural frameworks and key parameters reported in published economic evaluations of treatments for chronic hepatitis C, and to use one such model to explore the impact of variability in key parameters on resulting ICERs.

Methods

Literature Review

Structured searches of Medline, Medline (R) In-Process, Embase, Embase In-Process, the Cochrane Library, Health Economic Evaluation Database (HEED), and the National Health Service Economic Evaluation Database (NHS EED) were conducted between 2000 and 2009. All searches were conducted between June 29 and July 3, 2009, except for HEED, which was searched on August 17, 2009. The searches were re-run on May 3, 2011 to identify any additional relevant studies. The search strategy was designed to capture all relevant articles, and included both free text terms and MeSH headings (or equivalent for use in Embase) relating to hepatitis C and economic evaluations. Key terms included: hepatitis C, costs and cost analysis, economics, and quality-adjusted life years (see Appendix Table 1 in the Supplemental Materials available at doi:10.1016/j.jval.2011.06.006).

All identified citations were reviewed against the objectives using a process of positive exclusion, first considering just titles and/or abstracts and subsequently reviewing full text articles. The appropriate inclusion criteria were as follows: 1) study population of adult patients (aged >18 years or described as adult in the study methods) with chronic hepatitis C; 2) primary economic evaluation or systematic review of economic evaluations comparing treatments for chronic hepatitis C (studies assessing cost of illness, burden of disease, or the cost-effectiveness of screening programs were excluded); and 3) English language and published between 2000 and 2011. Only studies described as cost-utility analyses were included in our review; studies were excluded if they did not incorporate measures of quality of life (expressed as utilities). For the purposes of making comparisons across studies, those that did not present disaggregated data for any of the parameters of interest in a format that could be extracted and thus compared were excluded prior to data extraction. Likewise, studies that modeled a patient population coinfected with HIV, or a population recruited specifically because they experienced recurrent hepatitis C following transplant, were excluded prior to data extraction.

Data regarding the structural framework and key values for model parameters were extracted, where available, from those articles meeting the inclusion criteria. The data extraction of model parameters included: rates of disease progression (transition rates), values for health-related quality of life (expressed as utilities), and mean annual costs of care for each health state. Where there were multiple values for one health state reported, those values that represented a male patient aged 40 to 45 years with genotype 1 HCV were extracted for inclusion in the analysis. The number of different values identified for each health state for each aspect was used to calculate a mean, and was captured alongside the minimum and maximum value. Extracted values were qualitatively assessed; meta-analyses and/or statistical pooling of the extracted data were not undertaken, and were not deemed necessary to meet the objectives of this study. Study results and/or ICERs have not been extracted as they have largely been reviewed elsewhere [7,13] and are not the subject of this review. For comparative purposes, all costs were converted and inflated to 2008 US dollars using purchasing power parities and exchange rates appropriate to the year of analysis [14].

Analytic Decision Model

The impact on ICERs of altering values for key model parameters across the range identified by this review was assessed using a life-time Markov decision model based on the design and assumptions from a previously published model [15]. This model was chosen because of its simplicity of approach (including that it was developed in, and could be easily replicated in, Microsoft Excel [Microsoft Corporation, Redmond, WA]) and the completeness of reporting in the publication. To ensure consistency with the original model, the results were validated against those presented in the publication using the same data input values and assumptions. To illustrate the impact of the variability in model parameters used by the studies identified by this review in a quantitative manner, a base case was chosen that compared a treatment strategy of peginterferon alfa plus ribavirin with interferon alfa plus ribavirin. As with the published model, treatment was for a maximum of 48 weeks, with those patients not exhibiting an early virological response (EVR) ceasing treatment at 12 weeks. The base-case analysis included a cohort of 1000, treatment-naïve, male patients, with an average age of 45 years, with genotype 1 HCV and without pre-existing cirrhosis.

Values for key model parameters (rates of disease progression, utilities, and costs) were altered according to the mean, minimum, and maximum values identified in this review to assess the impact on overall results. The following three analyses were conducted: 1) the mean values for each input parameter; 2) equivalence to a least favorable scenario for treatment with peginterferon alfa plus ribavirin, that is, using the minimum values for rates of disease progression and costs associated with each health state and the maximum values for utility associated with each health state (except for the utility of the SVR health state, which used the minimum identified value); and 3) equivalence to a most favorable scenario for treatment with peginterferon alfa plus ribavirin, that is, using the maximum values for rates of disease progression and cost and the minimum values for utility (except for the utility of the SVR health state which used the maximum identified value). During the analysis the efficacy (proportion of patients achieving SVR) and the drug acquisition costs were kept constant (i.e., the effectiveness and drug acquisition costs of the comparative treatment strategies were not altered). The values for SVR and drug costs were taken from the publication of the original model [15]. Only those values for health states included in the published model were included in this analysis.

Results

Overview

In total, 3237 individual citations were identified by the searches, resulting in 34 publications of economic evaluations describing the cost-effectiveness of treatments for chronic hepatitis C that were found to meet the inclusion criteria and were suitable for data extraction (Fig. 1) [15–48]. The updated searches identified a further 341 individual citations for review, of which 4 met the inclusion criteria [49–52]. These four have not been incorporated into the analysis because they do not contain any additional model parameters to those already identified, and hence do not affect the results. The basic characteristics of the included studies are presented in Appendix Table 2 in the Supplemental Materials available at doi:10.1016/j.jval.2011.06.006.

Overall, the findings of this review suggest that, despite the relatively large number of publications in this area, most are based