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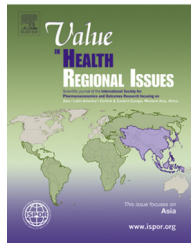

Assessing the Budget Impact and Economic Outcomes of the Introduction of Daclatasvir + Asunaprevir and Sofosbuvir/Ledipasvir for the Treatment of Chronic Hepatitis C Virus Infection in Japan

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ABSTRACT

Background: The advent of highly efficacious, well-tolerated, all-oral direct-acting antiviral regimens has revolutionized the standard of care for patients chronically infected with hepatitis C virus. As efficacy and safety rates converge, prescribers and payers need to consider value for money. **Objectives:** To evaluate the health economic value of daclatasvir + asunaprevir versus sofosbuvir/ledipasvir via a cost-effectiveness analysis, and determine the optimal treatment considering both costs and health outcomes in Japan. **Methods:** A previously published Markov model was used to estimate the cost-effectiveness of daclatasvir + asunaprevir compared with sofosbuvir/ledipasvir on the basis of a matching-adjusted indirect comparison of pivotal trials and modeling inputs specific to the Japanese setting. A de novo budget impact model was developed and used to predict the cost implications of differing treatment sequences. **Results:** Cost-effectiveness results demonstrated minimal difference in terms of benefit (0.037 fewer QALYs and 0.014 fewer life-years with daclatasvir + asunaprevir); nevertheless, a significant difference in cost was predicted (estimated ¥2,299,700 [US $21,695] reduction with daclatasvir + asunaprevir). The budget impact analysis estimated that treatment with daclatasvir + asunaprevir is expected to be less expensive than treatment with sofosbuvir/ledipasvir (as the proportion of patients initially treated with sofosbuvir/ledipasvir increased from 0% to 100%, total costs increased from ¥206 to ¥403 billion [US $1.94 billion to US $3.80 billion]). **Conclusions:** On the basis of results from an established cost-effectiveness model and a conventional budget impact analysis, treatment with daclatasvir + asunaprevir is expected to be cost-saving compared with treatment with sofosbuvir/ledipasvir in Japan with similar health outcomes, regardless of treatment sequence.

Keywords: asunaprevir, budget impact, cost-effectiveness, daclatasvir, hepatitis C virus.

Introduction

The hepatitis C virus (HCV) infection is a blood-borne infection that targets the cells of the liver. If left untreated, chronic hepatitis C can lead to life-threatening end-stage liver disease complications, including decompensated cirrhosis and hepatocellular carcinoma (HCC) [1].

The incidence of HCV infection is often difficult to establish because of the asymptomatic nature of the disease in its early stages; nevertheless, an estimated 1.5 million to 2 million people are infected in Japan [2], with HCV genotype 1b accounting for approximately 70% of cases [3,4]. Here, the prevalence of HCV infection is remarkably high in people older than 65 years, suggested to be due to the rates of transmission peaking during the 1960s and 1970s [5–7]. More recent estimates of incidence are relatively low at 1.8 to 3.4 per 100,000 person-year [6]. As a result, the Japanese cohort is generally at more advanced stages of the disease (complicated by the fact that increasing age is a risk factor for HCC [2]), and is largely pretreated [5,8]. In these patients, interferon-based treatment is less likely to be effective or, because of substantial contraindications and tolerability issues, may be precluded [9–14].

Achieving a sustained virologic response (SVR) after treatment corresponds to cure in 99% of patients and is associated with improved quality of life, regression of fibrosis, and reduced risk of liver-related complications [15–17]. Novel all-oral direct-acting antiviral (DAA) regimens have been shown to provide efficacious and well-tolerated treatment options. The DAA combination of

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daclatasvir and asunaprevir has demonstrated high efficacy for patients infected with HCV genotype 1b, and has provided a treatment option for those with high unmet need [18,19]. This regimen has also been shown to offer economic value versus conventional standard of care in Japan [20,21], and has therefore become the standard of care for those patients who are eligible.

As alternative DAA regimens are introduced, it is important to assess the economic impact on health care systems in terms of cost and patient benefit and contrast this to the present standard of care. Such information may then be used to determine optimal treatment strategies. This study aimed to 1) demonstrate the relative economic value of daclatasvir + asunaprevir versus sofosbuvir/ledipasvir via a conventional cost-effectiveness analysis and 2) assess the budget impact of the introduction of sofosbuvir/ledipasvir to the market, with a view to determining an optimal treatment strategy.

Methods

Population

Analyses focused on the treatment of patients who are infected with HCV genotype 1b and do not have nonstructural protein 5A (NS5A) resistant-associated polymorphisms (RAPs), according to the Japanese package insert and guideline for daclatasvir + asunaprevir.

Cost-Effectiveness Analysis

A published decision tree and Markov model (the MOdelling the NAtural histoRy and Cost-effectiveness of Hepatitis cost-effectiveness [MONARCH] model) that has previously been described in detail and validated to the Japanese setting was used to estimate the costs and benefits associated with 24 weeks of treatment with daclatasvir + asunaprevir and 12 weeks of treatment with sofosbuvir/ledipasvir [20,22–25]. The model runs in annual cycles over a variable time horizon, up to patient lifetime (maximum 80 years from start), with half-cycle correction applied. Patients enter the model at the chronic hepatitis C without cirrhosis health state or the compensated cirrhosis health state (or they may be distributed across the two), and may subsequently progress to decompensated cirrhosis, HCC, or death (Fig. 1). Simulation of the natural history of chronic hepatitis C is captured through the application of health state–specific disease transition rates, and the clinical and cost implications for each health state are informed by Japanese data (see Appendix Table 1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.vhri.2016.10.002). Because the cost of genetic testing for NS5A-associated RAPs is covered by the drug manufacturer, these have not been included in the analyses of expected costs to the payer in Japan.

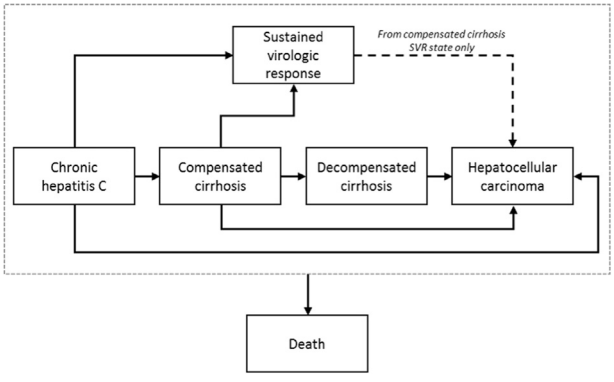

Fig. 1 – Flow diagram of MONARCH Markov model. SVR, sustained virologic response.

Treatment is initiated during the first year of the modeled time horizon and a decision tree is used to determine whether treatment is successful, defined according to rates of SVR. If treatment is successful, patients move to the SVR health state. On the basis of published probabilities and consistent with a previous study regarding the expected complication rates associated with the regimens of interest [20], it is assumed that patients who achieve SVR from the chronic hepatitis C state without cirrhosis remain in the SVR state for the duration of the simulation and do not incur further complications; nevertheless, a proportion of those who achieve SVR from the state of compensated cirrhosis will progress to HCC. In those subjects who do not achieve SVR, disease progression continues from whichever state they were in at initiation of antiviral therapy.

Efficacy data have been sourced from a matching-adjusted indirect comparison of data from Japanese patients without NS5A RAPs in the AI447-026 and AI447-031 studies for daclatasvir + asunaprevir and the GS-US-337-0113 study for sofosbuvir/ledipasvir [18,26–28]. To adjust for cross-trial differences, patient-level data (age, body mass index, sex, previous treatment experience, previous treatment response, interferon eligibility, HCV ribonucleic acid level, interleukin 28B genotype, cirrhosis status, alanine aminotransferase, albumin, and platelets) in the daclatasvir + asunaprevir trials were weighted to match reported summary baseline characteristics in the sofosbuvir/ledipasvir trial (see Appendix Table 2 in Supplemental Materials found at http://dx.doi.org/10.1016/j.vhri.2016.10.002). After adjustment for cross-trial differences, a nonstatistically significant difference of 0.7% in SVR was estimated between the daclatasvir + asunaprevir and the sofosbuvir/ledipasvir regimens (99.3% and 100%, respectively).

Treatment discontinuation was applied in the base-case analysis at a rate of 1.3% for daclatasvir + asunaprevir and 0% for sofosbuvir/ledipasvir, according to matching-adjusted indirect comparison data [28]. Drug unit prices were obtained from the Japan National Health Insurance drug price standard [29]; weekly acquisition costs were ¥55,320 (US $522) for daclatasvir, ¥39,864 (US $376) for asunaprevir, and ¥383,578 (US $3,619) for the combination tablet of sofosbuvir/ledipasvir. Adverse event rates are minimal and comparable across the two regimens [28], and are not expected to incur significant management costs; therefore, these were not incorporated in the base-case analysis.

A cohort of 1000 patients with a mean age of 69 years, 40.4% males and 24% with compensated cirrhosis, was simulated within the model until death, and predicted total HCV-related costs (treatment and complication management), life-years, and quality-adjusted life-years (QALYs) were recorded [30]. A government perspective has been adopted, with costs and health utility values discounted at an annual rate of 2%, in line with Japanese guidelines [31].

Probabilistic sensitivity analysis (PSA) was conducted to assess the impact of uncertainty in model input parameters and rates of SVR on economic outcomes. The analysis used a conventional probabilistic analysis approach in which all model input parameters are simultaneously sampled using appropriate statistical distributions. A beta distribution was used to sample proportions, a gamma distribution was used to sample costs, and a normal distribution was used to sample patient age. Because of the lack of informed variation in a 100% SVR rate (sofosbuvir/ledipasvir), the “rule of three” [32] was used to estimate the lower bound of a 95% confidence interval, which was subsequently used to inform the derivation of a standard error. Rates of SVR were then sampled using a normal distribution, assuming an upper limit of 100%. To remain consistent, the SVR rate