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.

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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 NSSA-associated RAPs is covered by the drug manufacturer, these have not been included in the analyses of expected costs to the payer in Japan.

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 NSSA 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 with HCV genotype 1b and do not have nonstructural protein 5A (NS5A) resistant-associated polymorphisms (RAPs), according to matching-adjusted induction data [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).

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” [22] 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
associated with daclatasvir + asunaprevir was also sampled using a normal distribution in a similar fashion.

**Budget Impact Analysis**

A budget impact analysis, conducted over a 3-year time horizon, assessing the cost implications of the introduction of sofosbuvir/ledipasvir to the Japanese market was conducted. The principle perspective of this analysis was to assess optimal treatment sequencing to minimize total cost impact.

For the purpose of this analysis, only daclatasvir + asunaprevir and sofosbuvir/ledipasvir were considered. The impact of treating relevant patients initially with sofosbuvir/ledipasvir followed by daclatasvir + asunaprevir for those failing to achieve SVR was contrasted with that of treating with daclatasvir + asunaprevir first followed by sofosbuvir/ledipasvir for treatment failures. SVRs were derived from the indirect comparison described earlier, and the market share of each initial treatment was varied from 0% to 100%. It was necessary to extrapolate uptake estimates for 2016 to 2018 on the basis of previous sales figures for daclatasvir + asunaprevir (see Results section).

Treatment and complication management costs were accumulated over the 3-year model time horizon. Patients not treated were not considered in the analysis because of their inability to influence incremental results.

**US Pricing Parity**

Results of both cost-effectiveness and budget impact analyses are also presented in US dollars, converted using the 2015 Organisation for Economic Co-operation and Development purchasing power parity comparisons (US $1 = ¥106) [33].

**Results**

**Cost-Effectiveness Analysis**

Incremental results, presented in Table 1, demonstrate minimal difference between the two treatments in terms of health outcomes: daclatasvir + asunaprevir resulted in 0.037 and 0.014 fewer discounted QALYs and life-years, respectively. In contrast, a significant difference in cost was estimated between the two regimens, with an expected ¥2,299,700 (US $21,695) reduction in total discounted cost associated with daclatasvir + asunaprevir compared with sofosbuvir/ledipasvir. Univariate sensitivity analyses (presented in Appendix Figures 1–3 in Supplemental Materials found at http://dx.doi.org/10.1016/j.vhri.2016.10.002) demonstrated that analysis conclusions are unlikely to be altered through reasonable changes in most of the input parameters, with the exception of therapy SVR rates, because of the similarity between treatments.

When accounting for joint parameter uncertainty in the model, the PSA output supports the indirect treatment comparison in relation to the nonsignificant difference between the two

<table>
<thead>
<tr>
<th>Absolute cost (¥)</th>
<th>LY</th>
<th>QALY</th>
<th>Incremental cost (¥)</th>
<th>LY</th>
<th>QALY</th>
<th>ICER (¥/LY)</th>
<th>ICER (¥/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daclatasvir + asunaprevir</td>
<td>2,897,710 (US $27,337)</td>
<td>14.544</td>
<td>13.787</td>
<td>Discounted</td>
<td>-2,299,700 (-US $21,695)</td>
<td>-0.014</td>
<td>-0.037</td>
</tr>
<tr>
<td>Sofosbuvir/ledipasvir</td>
<td>5,197,410 (US $49,032)</td>
<td>14.557</td>
<td>13.824</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Daclatasvir + asunaprevir</td>
<td>3,056,315 (US $28,833)</td>
<td>17.565</td>
<td>16.644</td>
<td>Nondiscounted</td>
<td>-2,289,315 (-US $21,597)</td>
<td>-0.019</td>
<td>-0.044</td>
</tr>
<tr>
<td>Sofosbuvir/ledipasvir</td>
<td>5,345,630 (US $50,430)</td>
<td>17.584</td>
<td>16.688</td>
<td></td>
<td></td>
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ICER, incremental cost-effectiveness ratio; LY, life-year; QALY, quality-adjusted life-year.
therapy regimes, as demonstrated in Figure 2. The PSA demonstrates a greater degree of uncertainty in relation to incremental QALYs compared with incremental life-years, with a 95% confidence interval of $0.067 to 0.044 for incremental QALYs and $–0.021 to 0.022 for incremental life-years. Relative to the absolute cost of each regimen, incremental costs were not estimated to vary by a significant degree.

**Budget Impact Analysis**

The derivation of the number of patients treated and achieving SVR, assuming 100% of patients receive either daclatasvir + asunaprevir or sofosbuvir/ledipasvir as an initial treatment, is presented in Figure 3; of the estimated 86,111 patients treated across 3 years (2016–2018), a total of 603 patients (on the basis of 0.7% failing to achieve SVR) would require re-treatment if initially treated with daclatasvir + asunaprevir, compared with 0 if initially treated with sofosbuvir/ledipasvir.

The relationship between total cost and the potential sequencing of treatment is presented in Figure 4. As the proportion of patients treated with sofosbuvir/ledipasvir increases from 0% to 100%, it is predicted that total costs (including treatment and complication management) would increase by more than two-fold, from ¥206 to ¥403 billion (US $1.94 billion to US $3.80 billion). The increase in cost is predominantly driven by the acquisition cost of initial treatment (¥197 billion to ¥396 billion; US $1.86 billion to US $3.74 billion). The expected cost associated with re-treating 603 patients with sofosbuvir/ledipasvir was estimated to be ¥2.77 billion (US $26.2 million). Results of sensitivity analyses are presented in Figure 5.

**Discussion**

With the introduction of novel all-oral DAA regimens with high but converging rates of efficacy and safety, it is important to determine which regimen offers the most value in economic terms. Results of this cost-effectiveness analysis demonstrate that though clinically daclatasvir + asunaprevir and sofosbuvir/ledipasvir do not differ significantly, large cost savings could be realized with the use of daclatasvir + asunaprevir.

The assessment of economic value is important from a decision-making context; nevertheless, consideration of the potential budget impact to the payer as a result of the introduction of alternative DAA regimens is also vital, given the cost concerns surrounding these treatments. The daclatasvir + asunaprevir regimen has been available for use in Japan since September 2014; assessing the impact of the introduction of sofosbuvir/ledipasvir to the present paradigm is important to inform on appropriate allocation of resources. Analyses presented demonstrate that the introduction of sofosbuvir/ledipasvir is expected to result in a large increase in spending in Japan, predominantly because of the higher acquisition cost compared with daclatasvir + asunaprevir. This is true regardless of the sequencing strategy applied, because the cost of re-treatment for patients who do not achieve SVR with daclatasvir + asunaprevir is still substantially lower than the cost of initially treating these patients (assuming no failures) with sofosbuvir/ledipasvir. The daclatasvir + asunaprevir regimen has previously demonstrated clinical and cost-effectiveness in important patient cohorts in the Japanese HCV population, including those who are elderly and/or cirrhotic; therefore, the implementation of an alternative regimen with significant costs should be considered in the context of clinical need.
SVR and treatment acquisition cost are key drivers of cost-effectiveness for chronic hepatitis C treatments. Because of the relatively small population sizes recruited to the clinical trials that informed the indirect comparison, some uncertainty in the estimation of clinical benefit may exist; the data used in this analysis are, however, supported by larger global trials of the regimens under consideration. Furthermore, the analysis of uncertainty undertaken for this study, particularly in relation to rates of SVR, demonstrated that the overall findings were robust. A simplifying pragmatic assumption implemented for this study was made in relation to the exclusion of costs of managing adverse events; this assumption is expected to have minimal impact on the results and has previously been shown not to have a substantial influence on overall cost-effectiveness conclusions in evaluations of DAAs [34]. All modeling inputs are Japanese-specific, and precedent for their use in Japanese cost-effectiveness analyses exists. Therefore, results of the cost-effectiveness analyses can be considered relatively robust.

Uncertainty in data, especially because extrapolation of uptake was required, may lead to overestimation or underestimation of the actual budget impact; therefore, it was important to test the impact of variation in values used. This demonstrated that results were most sensitive to SVR and uptake rates; nevertheless, no changes applied affected the conclusions of the analysis. Therefore, it is considered sensible to conclude that treatment should be offered with daclatasvir + asunaprevir in the first instance for patients with HCV without NSSA RAPs, reserving sofosbuvir/ledipasvir for those few patients who may fail to achieve SVR. From a generalized population perspective, this conclusion appears straightforward; nevertheless, the analysis does not consider the relative merits of a shorter regimen duration, which may be appropriate for specific types of patients (i.e., those who are difficult to access). Such benefits are difficult to quantify as part of a conventional cost-effectiveness analysis, and have therefore not been included.

It should be noted that patient co-payment has not been incorporated into the analysis because this is dependent on personal circumstances and therefore cannot be accurately reflected in a cohort analysis. Patient co-payment is higher for daclatasvir + asunaprevir; therefore, a larger contribution will be required from the government and health insurance provider for sofosbuvir/ledipasvir. In addition, societal costs were not considered in this analysis because of a paucity of appropriate data; several Japanese studies, however, have demonstrated significant increases in presenteeism, absenteeism, and lost productivity associated with HCV infection [35,36]. The introduction of DAAs is likely to contribute to a considerable reduction in societal burden, because of shorter treatment durations and a lesser need for clinical management. Furthermore, with the introduction of treatments capable of SVR rates approaching 100% in even the most difficult-to-treat patients, there is the very real potential to eradicate HCV infection completely, effectively eliminating any future burden associated with the disease, although such a strategy is likely to require significant financial and human investment.

As other new DAA regimens are introduced, their relative cost-effectiveness and absolute budget impact should be assessed against presently available treatment options, including daclatasvir + asunaprevir and sofosbuvir/ledipasvir.

On the basis of estimates of cost-effectiveness and budget impact in a Japanese context, treatment with daclatasvir + asunaprevir is expected to be cost-saving compared with treatment with sofosbuvir/ledipasvir in Japan for patients with HCV without NSSA RAPs, regardless of the treatment sequence.

Source of financial support: Funding for research and writing of this article was provided by Bristol-Myers KK. Publication of the study results is not contingent on the sponsor’s approval or censorship of the article.

**Fig. 5 – Budget impact sensitivity analysis. SVR, sustained virologic response.**

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**Supplementary Materials**

Supplemental material accompanying this article can be found in the online version as a hyperlink athttp://dx.doi.org/10.1016/j.vhri.2016.10.002 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

**REFERENCES**


