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Estimating the Long-Term Clinical and Economic Outcomes of Daclatasvir Plus Asunaprevir in Difficult-to-Treat Japanese Patients Chronically Infected with Hepatitis C Genotype 1b

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ABSTRACT

Objectives: Japan has one of the highest endemic rates of hepatitis C virus (HCV) infection. Treatments in Japan are currently limited to interferon-alfa–based regimens, which are associated with tolerability and efficacy issues. A novel regimen combining two oral HCV therapies, daclatasvir and asunaprevir (DCV + ASV), has shown favorable results in Japanese patients with chronic genotype 1b HCV infection. Comparisons of clinical and economic outcomes associated with DCV + ASV treatment and current standards of care were investigated. **Methods:** The MOdelling the NAtural histoRy and Cost-effectiveness of Hepatitis cost-effectiveness model projected outcomes in 1000 patients aged 70 years with either chronic hepatitis C or compensated cirrhosis over a lifetime simulation. Japanese-specific disease transition rates were used, and discounting was applied annually at a rate of 2%. Efficacy data for DCV + ASV and telaprevir triple therapy (telaprevir + pegylated interferon-alfa + ribavirin [TVR + pegIFN-α/RBV]) were obtained from a Japanese subgroup analysis found within a global meta-analysis: sustained virological response rates of 74%, 85%, and 87% were reported for null responders (NRs), partial responders (PRs), and interferon-alfa–ineligible/intolerant patients, respectively, treated with DCV + ASV, and rates of 42% and 59% were reported for NRs and PRs, respectively, treated with TVR + pegIFN-α/RBV. **Results:** Initiating DCV + ASV treatment in patients in the chronic hepatitis C disease stage resulted in quality-adjusted life-year gains of 0.96 and 0.77 over TVR + pegIFN-α/RBV for NRs and PRs, respectively, and a gain of 2.61 in interferon-alfa–ineligible/intolerant patients over no treatment. Similarly, quality-adjusted life-year gains of 1.11, 0.90, and 3.05 were observed when initiating treatment in patients in the compensated cirrhosis stage. Cumulative lifetime events of decompensated cirrhosis, hepatocellular carcinoma, and liver-related mortality were reduced by up to 66, 115, and 128, respectively, with DCV + ASV treatment. **Conclusions:** There is a lack of successful therapies for patients with HCV who have previously failed to achieve sustained virological response or are ineligible for interferon-alfa–based therapies. Results demonstrate that the provision of an alternative, interferon-alfa–free regimen, such as DCV + ASV, offers significant value in terms of avoiding life-threatening liver complications and increasing patients' quality of life.

Keywords: asunaprevir, clinical effectiveness, daclatasvir, hepatitis C.

Introduction

The global burden of the hepatitis C virus (HCV) is significant, with an estimated 3% of the world's population chronically infected [1]. Japan has one of the highest endemic rates of HCV infection; approximately 2 million people are infected, predominately with genotype 1b, resulting in more than 30,000 liver-related deaths each year [2–4]. An interferon-alfa–based treatment regimen is the mainstay of therapy for HCV-infected individuals [5], with the aim of eradicating the infection and thereby preventing disease progression. The recognized clinical end point for HCV eradication is sustained virological response (SVR), and recent advances have given rise to SVR rates of the order of 70% in treatment-naive patients, using a triple therapy regimen consisting of pegylated interferon-alfa, ribavirin, and a protease inhibitor (e.g., telaprevir or boceprevir [6,7]). Interferon-alfa–based regimens, however, are associated with tolerability issues; adverse events commonly observed include anemia, pyrexia, rash, renal toxicity, and gastrointestinal-related disorders [8,9], and there remains a proportion of patients who do not achieve SVR, particularly if they are previous nonresponders. For those patients intolerant of or ineligible for interferon-alfa–based

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therapy, there is currently no approved treatment option and they remain at risk of developing life-threatening complications including decompensated cirrhosis (DC) and hepatocellular carcinoma (HCC).

An interferon-alfa–free, all-oral regimen comprising daclatasvir and asunaprevir has been investigated for the treatment of patients with HCV genotype 1b infection [10]. Both daclatasvir and asunaprevir have demonstrated robust antiviral activity, with no clinically meaningful pharmacokinetic interactions when coadministered [11]. This regimen presents a significant step forward in the treatment of HCV infection for both untreated patients and those intolerant of or ineligible for interferon-alfa–based regimens. Daclatasvir is a first-in-class NS5A replication complex inhibitor with potent pan-genotypic antiviral activity in vitro (HCV genotypes 1–6) [12], and asunaprevir is a selective NS3 protease inhibitor with antiviral activity against HCV genotypes 1, 4, 5, and 6 in vitro [13].

This study aimed to model the lifetime clinical and economic outcomes associated with the use of daclatasvir combined with asunaprevir (DCV + ASV) for the treatment of patients with chronic HCV genotype 1b infection, specifically in a Japanese setting, who are either intolerant of or ineligible for interferon-alfa–based therapies, and those who did not respond to previous interferon-alfa–based treatment. Comparisons against current treatment options were made: telaprevir combined with pegylated interferon-alfa and ribavirin (TVR + pegIFN-α/RBV), pegylated interferon-alfa and ribavirin (pegIFN-α/RBV), and no treatment. Because of the relative lack of data associated with DCV + ASV treatment, sensitivity analyses were performed using efficacy rates derived from a global meta-analysis, with the intention of gaining a broader perspective of how DCV + ASV might perform in the clinical setting.

Methods

Model

The objective of this study was to compare the long-term clinical and economic outcomes of DCV + ASV with the current standard of care for chronic HCV genotype 1b infection in Japan. A modeling analysis was performed to predict the lifetime clinical and economic outcomes associated with DCV + ASV treatment using a previously published and validated computer cohort simulation model [14]. The model used (the MOdelling the NAtural histoRy and Cost-effectiveness of Hepatitis [MONARCH] model) is a cohort-based Markov lifetime simulation created in Microsoft Excel and designed to model the natural history of HCV and its complications [14–16]. The model runs in annual cycles over a variable time horizon, up to patient lifetime (80 years from start). Cohorts of 1000 patients are defined and enter the model at either the chronic hepatitis C (CHC) or the compensated cirrhosis (CC) disease stage. From here, those with CHC can progress to CC and all patients can progress to DC, HCC, death, or a state of SVR. The MONARCH model flow diagram is presented in Figure. 1. The model outputs total costs, incidence of clinical events, quality-adjusted life-years (QALYs), and life expectancy. Costs, QALYs, and life-years were all discounted at a rate of 2%, in line with current Japanese guidelines.

Disease transition rates are applied annually to the prevalent population in each health state to model the natural history of HCV. Patients who achieve SVR from the state of CHC remain in the state of SVR for the duration of the simulation, whereas those who achieve SVR from the state of CC may relapse and progress to HCC. In those subjects failing to respond to treatment, CHC progression continues from whichever disease stage they were in at initiation of antiviral therapy. All transition rates are drawn from recently published literature specific to the Japanese setting.

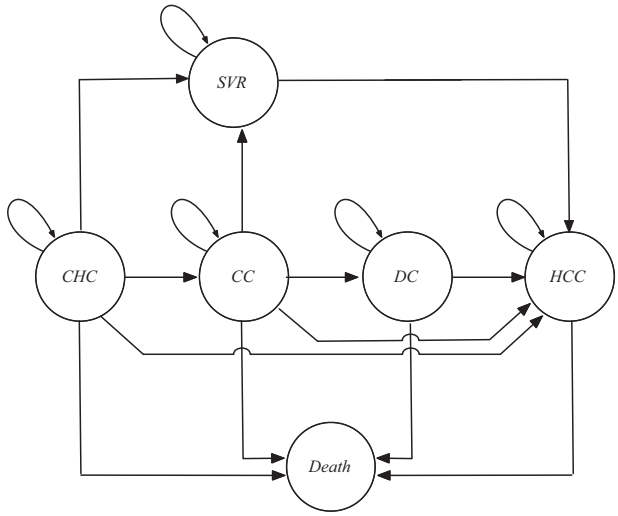

Fig. 1 – Flow diagram of the MONARCH model. CC, compensated cirrhosis; CHC, chronic hepatitis C; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; MONARCH, MOdelling the NAtural histoRy and Cost-effectiveness of Hepatitis; SVR, sustained virological response.

All-cause mortality is incorporated into the model via the use of Japanese-specific abridged life tables and affects patients in the CHC, CC, and SVR Markov states. The transition rates used in the model are presented in Table 1.

Health states within the model are subject to specific cost and utility values, applied annually. Health state utility values were obtained from the literature. To estimate health state costs, 10 Japanese hepatologists were surveyed between March 2013 and May 2013. Information regarding the treatment of CHC and CC in clinical practice was collected, including the treatments used, clinical tests, frequency of examinations, and adverse events. This information was then pooled and translated into costs; unit prices for disease management, clinical tests performed, and treatments prescribed were derived from the medical service fee or National Health Insurance price list. All costs and health utility

Table 1 – Disease transition rates.

Transition (genotype 1b)	Mean (SE)	Source
CHC to CC	0.065 (0.011)	Nakamura et al. [23]
CHC to HCC	0.016 (0.004)	Nakamura et al. [23]
CC to DC	0.021 (0.006)	Imazeki et al. [24]
CC to HCC	0.043 (0.008)	Hayashida et al. [25]
DC to HCC	0.083 (0.022)	Nakamura et al. [23]
DC to death	0.153 (0.017)	Nakamura et al. [23]
HCC to death	0.200 (0.012)	Nakamura et al. [23]
CC SVR to HCC	0.018 (0.011)	Arase et al. [26]

CC, compensated cirrhosis; CHC, chronic hepatitis C; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; SE, standard error.