博士論文（要約）

Cost–utility analysis of ledipasvir/sofosbuvir and sofosbuvir for the treatment of chronic hepatitis C in Japan -using a Markov state-transition model (日本における C 型慢性肝炎に対するレジパスビル/ソホスブビルとソホスブビルの費用効用分析 -マルコフ状態移行モデルを用いて)

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Backgroud

Chronic infection with the hepatitis C virus (HCV) is a serious, progressive, and often life-threatening disease affecting an estimated 1.3 to 2.4 million people in Japan. It is estimated that approximately 15% to 30% of patients in Japan with chronic hepatitis C (CHC) will develop complications, including liver cirrhosis, hepatocellular carcinoma (HCC) and end-stage liver disease. In Japan, approximately 70% to 80% of infections are associated with Genotype (GT) 1 HCV and approximately 20% to 30% with GT2 HCV.

For the treatment of GT1 CHC, pegylated interferon (PEG-IFN) and ribavirin (RBV) was long the standard of care in Japan. In 2011 and 2013, telaprevir (TVR) and simeprevir (SMV) in triple therapy with PEG-IFN and RBV were approved. The first IFN-free therapy was daclatasvir (DCV) with asunaprevir (ASV) approved in 2014. After DCV and ASV, the single tablet combination of ledipasvir (LDV) and sofosbuvir (SOF) has become available IFN-free treatment and was approved in 2015. For the treatment of GT2 CHC, the standard of care in many years was PEG-IFN and RBV. Recently in 2015, SOF has been approved in Japan for use in combination with RBV for the treatment of GT2 HCV as the first IFN-free regimen.

Both LDV/SOF for GT1 and SOF+RBV for GT2 HCV treatment have shown higher SVR rates than previous IFN-based therapy in the clinical trials conducted in Japan, and offered important options for patients who are ineligible for IFN. However, LDV/SOF and SOF have much higher treatment costs than other treatment options. Therefore, from the perspective of healthcare decision makers, cost-effectiveness data is needed to assess whether additional expenditures for LDV/SOF and SOF would result in additional clinical benefit.

Objective

The objective of this study is to assess the cost-effectiveness of LDV/SOF for GT1 CHC and SOF+RBV for GT2 CHC treatment in Japan, using a markov state transition model and the cost and outcome data generated from Japan.

Methods and results

1) Adjustment of the Cure model and the validation of the adjusted model

The Cure model was developed from the model that was used in UK for NICE, and has been used in a published cost-effectiveness study for sofosbuvir in the treatment of CHC. The Cure model included 9 relevant health states (non-cirrhotic, cirrhotic, non-cirrhotic SVR, cirrhotic SVR, HCC, etc.)

The Cure model was adjusted for the cost-effectiveness study in Japan by replacing the transition probabilities mainly reported from Japanese clinical literature. Annual mortality rates were obtained from the Statistics Department of the Ministry of Health, Labour and Welfare. Cost and outcomes were discounted at 2%.

The validity of the adjusted model was evaluated by the comparision of survival rates and HCC incidence rates from model estimations and epidemiological literature.

2) Target population & treatment options

For GT1 HCV, four patient subgroups were considered: a) treatment-naïve (TN) non-cirrhotic, b) TN cirrhotic, c) Treatment-experienced (TE) non-cirrhotic, d) TE cirrhotic.

For GT2 HCV, four patient subgroups were considered: a) TN interferon eligible (IE), b) TN unsuitable for interferon (UI), 3) TE IE, 4) TE UI. For each subgroup, the proportion of patients initiating treatment at the non-cirrhotic stage was set to 82%.

Treatment options as comparators were selected based on the most recent HCV treatment guidelines for Japan.

3) Efficacy, utility and costs data

SVR rates of different therapies from Japanese and international clinical trials were used in the model. Utilities related to each health state and the utility changes related to antivirus treatments were obtained from Japanese studies.

Drug costs were derived from the 2015 National Drug Tariff. No treatment-related adverse events costs were included in this analysis due to data scarcity. Hospitalization costs and monitoring costs during the treatment, costs related with each health state were estimated based on published Japanese literature. Indirect costs, including productivity losses in terms of absenteeism and presenteeism, were also included in scenario analysis.

5) Model outcomes

The primary outcome measure was quality-adjusted life years (QALYs) gained. Life years (LYs) gained was a secondary outcome. Incremental cost-effectiveness ratio (ICER) per QALY and per LY was calculated.

6) Sensitivity analyses

Both a deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA) were conducted.

7) Budget impact analyses

The weight and patient number of each subgroup of GT1 and 2 CHC was estimated. The additional costs invested for LDV/SOF and SOF+RBV treatments, and the additional total direct costs compared with other treatments in each subgroup from the model analysis were used to multiply the patient number, to calculate the total budget impact of introducing LDV/SOF and SOF+RBV. Moreover, the comparators, patient numbers, and other parameters were varied to conduct scenario analyses for the budget impact analyses.

Results

1) Validity of the adjusted model

The adjusted model was developed and its validity has been confirmed. Between model estimations and literature reported data, the absolute differences in survival rates (5~15 years) were 2.4%~5.8%, while the absolute differences in HCC incidence rates (5~15 years) were 1%~5.6%.

2) Cost-utility of LDV/SOF for the treatment of GT1 CHC

LDV/SOF was found to have improved all the health related outcomes in all the patient subgroups, including QALYs, LYs, and the incidence of HCC and DCC, compared with other treatment options (PEGIFN+RBV, SMV+PEGIFN+RBV, TVR+ PEGIFN+RBV,

DCV+ASV, No treatment). The ICER (JPY/QALY) of LDV/SOF compared with SMV+PEGIFN+RBV in TN non-cirrhotic subgroup was calculated as: 6,097,686. In other three subgroups compared with DCV+ASV, the ICER (JPY/QALY) of LDV/SOF was caluculated as 2,853,483 (TN, cirrhotic), 2,015,836 (TE, non-cirrhotic), 1,553,448 (TE, cirrhotic). The robustness of the analysis results has been shown in DSA and PSA.

The additional costs invested for treatment, and the additional total direct costs of introducing LDV/SOF were estimated to be 2.89 and 2.37 trillion JPY.

3) Cost-utility of LDV/SOF for the treatment of GT1 CHC

SOF+RBV was found to have improved all the health related outcomes in all the patient subgroups, including QALYs, LYs, and the incidence of HCC and DCC, compared with other treatment options (PEGIFN+RBV, TVR+PEGIFN+RBV, No treatment). The ICER (JPY/QALY) of SOF+RBV compared with PEGIFN+RBV in TN, IE subgroup and TE, IE was calculated as: 2,148,465 and 494,049, respectively. In TN, UI and TE, UI subgroup, SOF+RBV was dominant compared with no treatment (less costs, more effective). The ICER (JPY/QALY) of LDV/SOF compared with TVR+PEGIFN+RBV in TE, IE, and non-cirrhotic subgroup was caluculated as 3,540,914. The robustness of the analysis results has been shown in DSA and PSA.

The additional costs invested for treatment, and the additional total direct costs of introducing SOF+RBV were estimated to be 1.38 and 0.14 trillion JPY.

Conclusion

Both LDV/SOF for GT1 and SOF+RBV for GT2 HCV treatment were considered to be cost-effective options in Japan against other treatments. Moreover, the interferon-free nature of LDV/SOF and SOF+RBV has a key advantage in terms of better treatment tolerability, fewer adverse events and shorter treatment duration.

The evidence generated from this research provided more support for the rational decision-making on the drug prices and health insurance strategies in this field in future.