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The cost-effectiveness of testing for NS5a resistance-associated polymorphisms at baseline in genotype 1a-infected (treatment-naïve and treatment-experienced) subjects treated with all-oral elbasvir/grazoprevir regimens in the United States

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SUMMARY

Background
The presence of baseline NS5A resistance-associated variants (RAVs) impacted treatment response in HCV genotype 1a (GT1a)-infected patients treated with elbasvir/grazoprevir (EBR/GZR) for 12 weeks, but not patients treated with EBR/GZR and ribavirin (RBV) for 16 weeks.

Aims
To assess the cost-effectiveness of baseline testing for NS5A RAVs in EBR/GZR-treated patients compared without testing, and with current treatments for GT1a patients.

Methods
We simulated the course of treatment with EBR/GZR, ledipasvir/sofosbuvir (LDV/SOF) and ombitasvir/paritaprevir/ritonavir+dasabuvir (3D) with or without RBV and natural history of disease of GT1a patients. Treatment-related data from clinical trials were used in a state-transition model of the natural history of chronic HCV GT1a infection and liver disease to project lifetime costs (US$2015) and quality-adjusted life years (QALY). Other clinical and economic inputs were estimated from published sources. We conducted base case and sensitivity analyses.

Results
RAVs testing-guided treatment with EBR/GZR resulted in more QALYs than EBR/GZR without testing, 3D+RBV, or LDV/SOF8. This strategy was cost-saving relative to 3D+RBV or LDV/SOF8 and was cost-effective compared with EBR/GZR without testing. LDV/SOF12 was not cost-effective compared with the EBR/GZR RAVs testing-based strategy. Treatment with EBR/GZR guided by RAVs testing is the most effective regimen among treatment-experienced patients without cirrhosis and cirrhotic patients. In sensitivity analysis, RAVs testing was cost-effective in 48–55% and 63–85% among noncirrhotic and cirrhotic patients respectively.

Conclusions
RAVs testing before treatment with EBR/GZR is likely to be a cost-effective alternative to the use of EBR/GZR without testing, LDV/SOF, or 3D among GT1a treatment-naïve or treatment-experienced patients.

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INTRODUCTION

Chronic infection with hepatitis C virus (HCV) causes significant morbidity, mortality and costs in the USA.[1] There is a wide variation in the genotype distribution of HCV infection by countries. In the USA, genotype 1 (GT1) predominates (75.3%), with subtype 1a (GT1a) being the most prevalent subtype.[2] There has been also a temporal shift towards more predominance of genotype 1a compared with genotype 1b in the USA.

Estimates of prevalence of NS5A resistance-associated variants (RAVs) vary by study, the method of detection, and the cuff value for determining resistance. In phase 2 or 3 programme, RAVs prevalence among GT1a patients from the USA, defined as any change from reference identified by population sequencing at NS5A amino acid positions 28, 30, 31 or 93, was estimated at 12% for elbasvir/grazoprevir (EBR/GZR).[3, 4] RAVs prevalence identified by population sequencing at positions 24, 28, 30, 31 or 93 was 13% in the ledipasvir/sofosbuvir (LDV/SOF) with ribavirin (RBV) clinical trial studies.[5, 6]

Baseline presence of NS5A RAVs can attenuate the efficacy of new direct-acting antivirals.[6–8] For example, when assessing the relevance of baseline NS5A RAVs from samples of treatment-naive patients or prior relapsers with HCV genotype 1a using a population sequencing assay, Jacobson *et al.*[9] found that baseline NS5A RAVs reduced the efficacy of the EBR/GZR regimen (12 weeks, no RBV) from 98% (345/352) to 86% (74/86). There was no impact of baseline NS5A RAVs on efficacy among patients who received EBR/GZR+RBV (16 weeks, with RBV).[9]

Testing for RAVs among some patients (e.g. with cirrhosis) is recommended by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) prior to selecting the next HCV treatment regimen.[10] Once the RAVs status of the patients has been determined, it is not clear what should be the optimal treatment regimen for patients with a given RAVs status.[11]

By increasing the expected sustained virological response (SVR) rates, the use of testing has the potential of influencing the course of the disease, thereby further reducing the incidence of liver-related complications, deaths and associated disease management costs. However, testing all GT1a patients at baseline introduces additional costs, and whether regimens based on RAVs testing provide sufficient value remains to be determined. The main objective of our study was to assess the cost-effectiveness of baseline testing for NS5A RAVs in EBR/GZR-treated patients compared without testing and with current treatments for GT1a patients in the USA.

MATERIALS AND METHODS

Model overview and assumptions

We developed a Semi-Markov state-transition cohort disease simulation model that synthesised epidemiological, clinical and economic data to estimate the expected lifetime costs and quality-adjusted life-years (QALYs) associated with and without baseline testing for NS5A RAVs in EBR/GZR-treated patients and with current treatments for GT1a patients. The model simulates the treatment regimens as well as the natural history of chronic HCV and predicts the lifetime incidence of end-stage liver disease and death. The model is consistent with the current understanding of the biology of chronic HCV- and liver disease and their treatment; is similar to other published cost-effectiveness models of HCV disease,[12–16] including our previously published and validated Markov cohort model[17–19]; and its development and analysis follow accepted best practices.[20]

The state-transition model consists of several health states (Figure 1). The severity of chronic HCV infection is described by the degree of fibrosis using the METAVIR scoring system: no fibrosis (F0), portal fibrosis without septa (F1), portal fibrosis with few septa (F2), numerous septa without fibrosis (F3), and compensated cirrhosis (F4).

A subject with a given fibrosis score may progress to more severe stages of liver disease or may remain in that health state. In the absence of successful treatment, regression to less severe health states is not permitted. However, after a successful treatment, a subject can achieve a sustained virological response. To account for the possibility of HCV reinfection among high-risk patients, the model allows for transitions from sustained virological response states to fibrosis states following reinfection and failure to clear the virus during the acute infection state. Only one-time reinfection was considered and future diagnosis and treatment was not accounted for.

Patients with compensated cirrhosis are at risk for developing decompensated cirrhosis and hepatocellular carcinoma. If a patient develops decompensated cirrhosis and/or hepatocellular carcinoma then the patient may receive a liver transplant. Decompensated cirrhosis, hepatocellular carcinoma and liver transplant patients are subjected to excess mortality compared with the general population. To account for different mortality rates of

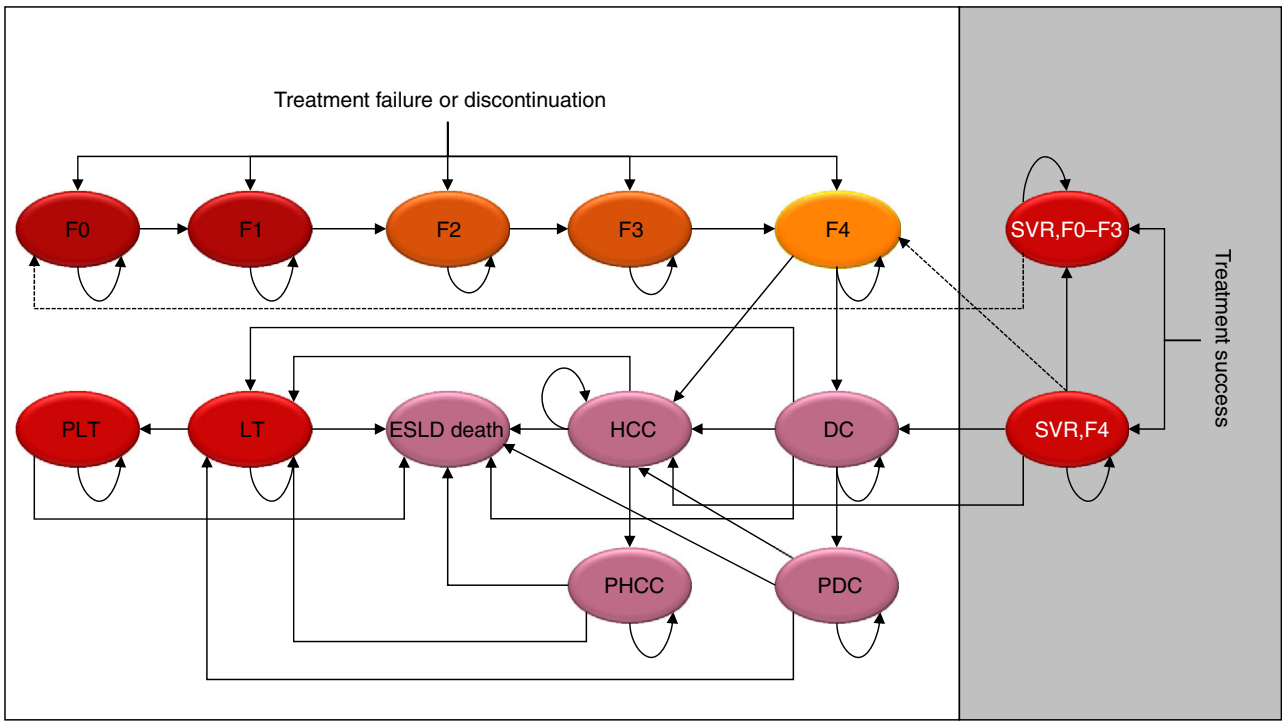

Figure 1 | State-transition diagram for chronic hepatitis C and liver disease model. The model consists of the following health states: no fibrosis (F0), portal fibrosis without septa (F1), portal fibrosis with few septa (F2), portal fibrosis with numerous septa without cirrhosis (F3), compensated cirrhosis (F4), two decompensated cirrhosis (DC) states – first year and subsequent years (PDC), two hepatocellular carcinoma (HCC) states – first year and subsequent years (PHCC), two liver transplant states – first year (LT) and subsequent years (PLT), End-stage liver disease death (ELDS Death), death from all other causes (not shown here), and two sustained virological response (SVR) status states stratified by fibrosis stage – 'SVR, F0–F3' and 'SVR, F4'.

decompensated cirrhosis, hepatocellular carcinoma and liver transplantation during the first year and subsequent years, each of these health states was divided into two states: first-year state and subsequent-years state. All other patients face the same mortality risk as the general population.

The model simulates the RAVs testing treatment strategies and 12-week follow-up and the natural history of HCV. The treatment and follow-up period is not modelled separately from the natural history model. To simplify, the treatment phase of the model representing treatment and follow-up period just determines whether a patient is either cured or not. The Markov part of the model is simulated using a cycle length of 1 year.

Testing and treatment comparators

EBR/GZR is indicated with or without ribavirin for treatment of chronic HCV genotypes 1 or 4 infection in adults. Testing for presence of NS5A RAVs polymorphisms at amino acid positions 28, 30, 31 or 93 prior to initiation of therapy is recommended for GT1a patients. In the clinical trials of EBR/GZR, the analyses were conducted using population nucleotide sequencing. Based on the test results, treatment-naïve or PegIFN/RBV-experienced GT1a patients without baseline NS5A polymorphisms are treated with EBR/GZR for 12 weeks whereas those with baseline NS5A polymorphisms are treated with EBR/GZR and RBV for 16 weeks.[3, 10]

We consider four regimens: (i) EBR/GZR without any RAVs-based testing (EBR/GZR+NoTesting), (ii) EBR/GZR with RAVs-based testing (EBR/GZR+Testing), LDV/SOF, and ombitasvir/paritaprevir/ritonavir and dasabuvir (3D) with or without ribavirin (Table 1). LDV/SOF regimens for treating naïve noncirrhotic patients with low viral load also included treatment for 8 weeks only. Per products' label, RAVs testing was not included in any of the LDV/SOF or 3D± RBV regimens.

Patient characteristics

The target population is patients infected with chronic hepatitis C virus genotype 1a with or without prior

Table 1 | Regimens and durations for treatment of HCV genotype 1a in patients with or without cirrhosis

Patient Population: Regimen	Duration (weeks)	SVR (*n*/*N*)	Range	Probability distribution	Reference
Treatment-naïve or PegIFN/RBV-experienced with and without cirrhosis, RAVs testing*					
Without baseline NS5A polymorphism†: EBR/GZR	12	0.980 (441/450)	0.962–0.991	Beta (440.02, 8.98)	3
With baseline NS5A polymorphism: EBR/GZR+RBV	16	1.000 (6/6)	0.541–1.000	Uniform (0, 1)$^{1/6}$	3
Treatment-naïve or PegIFN/RBV-experienced with and without cirrhosis, no testing*					
Without baseline NS5A polymorphism: EBR/GZR	12	0.980 (441/450)	0.962–0.991	Beta (440.02, 8.98)	3
With baseline NS5A polymorphism: EBR/GZR	12	0.70 (39/56)	0.559–0.812	Beta (38.30, 16.70)	3
Treatment-naïve without cirrhosis, no testing					
Without baseline NS5A polymorphism: LDV/SOF	8	0.965 (138/143)	0.92–0.989	Beta (137.03,4.97)	22
Without baseline NS5A polymorphism: LDV/SOF	12	0.983 (347/353)	0.963–0.994	Beta (346.02, 5.98)	22,23
Without baseline NS5A polymorphism: 3D+ RBV	12	0.957 (402/420)	0.933–0.974	Beta (401.04, 17.96)	26
With baseline NS5A polymorphism: LDV/SOF	8	0.938 (30/32)	0.92–0.989	Beta (137.03, 4.97)	22
With baseline NS5A polymorphism: LDV/SOF	12	0.989 (187/189)	0.963–0.994	Beta (346.02, 5.98)	22,23
With baseline NS5A polymorphism: 3D+ RBV	12	0.957 (402/420)	0.933–0.974	Beta (401.04, 17.96)	26
Treatment-naïve with cirrhosis, no testing					
Without baseline NS5A polymorphism: LDV/SOF	12	0.978 (45/46)	0.885–0.999	Beta (44.02, 0.98)	24,25
Without baseline NS5A polymorphism: 3D+ RBV	24	0.946 (53/56)	0.851–0.989	Beta (52.05, 2.95)	26
With baseline NS5A polymorphism: LDV/SOF	12	0.978 (45/46)	0.885–0.999	Beta (44.02, 0.98)	24,25
With baseline NS5A polymorphism: 3D+ RBV	24	0.946 (53/56)	0.851–0.989	Beta (52.05, 2.95)	26
PegIFN/RBV-treatment-experienced without cirrhosis, no testing					
Without baseline NS5A polymorphism: LDV/SOF	12	0.97 (353/161)	0.931–0.99	Beta (160.03, 4.97)	21,24,25
Without baseline NS5A polymorphism: 3D+ RBV	12	0.96 (420/166)	0.918–0.984	Beta (165.04, 6.96)	26
With baseline NS5A polymorphism: LDV/SOF	12	0.97 (353/161)	0.931–0.99	Beta (160.03, 4.97)	21,24,25
With baseline NS5A polymorphism: 3D+ RBV	12	0.96 (420/166)	0.918–0.984	Beta (165.04, 6.96)	26
PegIFN/RBV-treatment-experienced with cirrhosis, no testing					
Without baseline NS5A polymorphism: LDV/SOF+RBV	12	0.961 (53/74)	0.89–0.992	Beta (73.04, 2.96)	24,38
Without baseline NS5A polymorphism: LDV/SOF	24	0.98 (46/48)	0.891–0.999	Beta (47.02, 0.98)	24
Without baseline NS5A polymorphism: 3D+ RBV	24	0.954 (56/62)	0.871–0.99	Beta (61.05, 2.95)	26
With baseline NS5A polymorphism: LDV/SOF+RBV	12	0.961 (53/74)	0.89–0.992	Beta (73.04, 2.96)	24,38
With baseline NS5A polymorphism: LDV/SOF	24	0.98 (46/48)	0.891–0.999	Beta (47.02, 0.98)	24,38
With baseline NS5A polymorphism: 3D+ RBV	24	0.954 (56/62)	0.871–0.99	Beta (61.05, 2.95)	26

*Patients who have failed treatment with peginterferon alfa (PegIFN) + ribavirin (RBV). Because the presence HCV NS5A amino acid polymorphisms was associated with reduced efficacy of EBR/GZR for 12 weeks regardless of prior treatment history or status, the SVR data were pooled across cirrhosis and prior treatment history status. EBR/GZR, elbasvir/grazoprevir; LDV/SOF, ledipasvir/sofosbuvir; 3D, ombitasvir/paritaprevir/ritonavir and dasabuvir; RBV, ribavirin.

†NS5A resistance-associated polymorphisms at amino acid positions 28, 30, 31 or 93.

treatment experience. The baseline patient characteristics for the analyses are based on published studies. Patient characteristics impact the efficacy of the treatment regimens, the rate of disease progression in patients who failed treatment, and annual mortality rate.

Treatment inputs

Information concerning the treatment regimens was derived from the clinical trials and the published literature. This includes the treatment efficacy, discontinuation rates and side effects associated with antiviral therapy.

The safety and efficacy of EBR/GZR were evaluated in 8 clinical trials in approximately 1800 subjects with genotype (GT) 1, 3, 4 or 6 chronic hepatitis C infection with compensated (with and without cirrhosis) liver disease. The efficacy of the other regimens was obtained from clinical trials of LDV/SOF and 3D± RBV.[21–26]

The discontinuation rates and safety metrics associated with using EBR/GZR were derived from indirect unadjusted comparisons rather than a network meta-analysis. Estimates of discontinuation rates and the probabilities of depression, anaemia and rash occurring during the use of any of the comparators were obtained from the Canadian Agency for Drugs and Technologies in Health Therapeutic Review.[27]

Clinical inputs

Estimates of fibrosis progression rates were based on a published meta-analysis.[28] Other clinical inputs are shown Table 2.

Cost inputs

The weekly wholesale acquisition costs of anti-viral therapies were obtained from the First DataBank.[29] Costs of NS5A RAVs testing were based on the national median reimbursement rate for commercial insurance plans as listed in the National Fee Analyzer by Optum[30] (Table 2). The cost of treating adverse events was obtained from a published study.[31]

The health state costs associated with disease progression (e.g. diagnostic tests, visits, hospitalisation) were based on the published literature (Table 2).

Health-related quality-of-life inputs

Utility weights during the treatment phase and for each of the HCV health states and liver disease conditions were used to adjust quality of life of survivors (Table 2). On-treatment, disutility was applied during the treatment period for regimens containing ribavirin. Disutility of treatment of 0.11 from a base utility of 0.77 for mild and 0.66 for moderate HCV was estimated by comparing patients treated with PegINF or RBV vs. no therapy using the EQ-5D instrument, resulting in an average treatment multiplier of 0.85.[32]

To avoid double counting the disutility of adverse events (as these are accounted for with the on-treatment disutility) no quality of life multipliers for anaemia, depression or rash were applied for the patients experiencing theses adverse events.

Model validation

The face validity of the model was checked during collaboration with clinicians, health economists and decision scientists, and by comparing its structure with that of previously published models.[12–16] Several tests were built into the model for verification and to ensure internal validity. For example, the sum of the distribution of persons in each health state at the end of each cycle was verified to be equal to 1 both numerically using Excel and analytically by transferring the formula into Mathematica and using the built-in algebraic functions within Mathematica to manipulate the resulting expressions. The model was also programmed in R and outcomes from the two programmes were compared. The results were the same (up to the rounding precision in the values). We cross-validated the model by comparing its prediction of a 20-year probability of compensated cirrhosis with that of previous models.[14, 33] These models predicted the 20-year probability of compensated cirrhosis among untreated 44-years-old patients with mild chronic HCV between 27% and 29%. Assuming that the respective distribution of mild HCV between F0 and F1 is 35% and 65%, the model projected the 20-year probability of compensated cirrhosis at 29.7%.

Model analysis

The model was run for each of the specified patient profiles. Depending on the type of analysis an overall weighted average of the results was generated based on the distribution of the patient characteristics assumed for a given analysis.

We applied within-cycle correction to all cumulative outcomes using Simpson's 1/3rd rule and tested sensitivity of the results to the method of correction by applying the standard application of half-cycle correction method.[34] For the cost-effectiveness analysis, we calculated costs and QALYs over the remaining duration of a patient's lifetime. Cost-effectiveness of an EBR/GZR regimen relative to a comparator was evaluated using the incremental cost-effectiveness ratio (ICER) obtained by dividing incremental total discounted costs by the incremental total discounted number of QALYs resulting from using EBR/GZR regimen instead of the comparator.

Base-case analysis

Aggregated results are presented separately by cirrhosis status and previous treatment history.

Subgroup analysis

The results are also provided separately by each fibrosis stage. The robustness of the results was also tested by changing the baseline demographic characteristics such as sex (i.e. men only and women only) and age distribution.

Deterministic sensitivity analysis

We conducted one-way deterministic sensitivity analysis for several parameters showing the effect of varying these inputs on the ICER of EBR/GZR treatment strategies compared with no testing. We varied progression rates,

Table 2 | Clinical and other inputs used in the analysis

	Base-case	Range	Probability distribution	Reference
Annual transition probabilities				
Fibrosis progression				28
F0 to F1	0.117	0.104–0.130	Beta (274.6, 2072.8)	
F1 to F2	0.085	0.075–0.096	Beta (230.3, 2478.8)	
F2 to F3	0.120	0.109–0.133	Beta (337.9, 2478.2)	
F3 to F4	0.116	0.104–0.129	Beta (292.3, 2227.8)	
Cirrhosis regression				
SVR, F4 to SVR, F3	0.086	0.047–0.142	Beta (11.67, 123.39)	39
Cirrhosis progression				
F4 to DC	0.029	0.010–0.039	Beta (14.89, 498.62)	40–45
F4 to HCC	0.028	0.010–0.079	Beta (2.43, 84.41)	39, 46–49
SVR, F4 to DC	0.008	0.002–0.036	Beta (0.84, 103.66)	45, 50
SVR, F4 to HCC	0.005	0.002–0.013	Beta (0.50, 251.98)	45, 50
Reinfection, high-risk patients				
Annual reinfection rate	0.024	0.009–0.061	Beta (3.19, 129.92)	51, 52
Probability of chronicity	0.75	0.364–0.793	Beta (11.91, 8.24)	53
Liver disease progression				
DC to HCC	0.068	0.030–0.083	Beta (23.51, 322.19)	54
Probability of receiving a liver transplant				
DC	0.023	0.010–0.062	Beta (1.42, 87.06)	55, 56
HCC	0.040	0.000–0.140	Beta (0.04, 5.18)	57
Mortality rates				
Age/sex-specific all-cause				58
DC (first year) mortality	0.140	0.065–0.190	Beta (16.44, 100.97)	54
DC (subsequent years) mortality	0.103	0.065–0.190	Beta (9.26, 80.61)	54
HCC-related mortality	0.427	0.330–0.860	Beta (5.29, 7.10)	40
LT (first year) mortality	0.166	0.060–0.420	Beta (2.56, 12.86)	59
LT (subsequent years) mortality	0.044	0.060–0.420	Beta (0.18, 3.81)	59
Adverse events per regimen				
Probability of depression				
Elbasvir/grazoprevir	0.019 (6/316)	0.007–0.041	Beta (5.98, 309.02)	3
Elbasvir/grazoprevir with Ribavirin	0.038 (4/106)	0.01–0.094	Beta (3.96, 101.04)	3
Ledipasvir/sofosbuvir	0.003	0–0.017	Beta (0.38, 145.46)	27
Ledipasvir/sofosbuvir with Ribavirin	0.084	0.022–0.28	Beta (1.42, 15.41)	27
3D + RBV	0.058	0.009–0.258	Beta (0.72, 11.72)	27
Probability of anaemia				
Elbasvir/grazoprevir	0.006 (2/316)	0.001–0.023	Beta (1.99, 313.01)	3
Elbasvir/grazoprevir with ribavirin	0.16 (17/106)	0.096–0.244	Beta (16.84, 88.16)	3
Ledipasvir/sofosbuvir	0.012	0.004–0.033	Beta (2.64, 219.04)	27
Ledipasvir/sofosbuvir with Ribavirin	0.060	0.024–0.129	Beta (4.56, 71.82)	27
3D + RBV	0.082	0.028–0.206	Beta (2.92, 32.79)	27
Probability of rash				
Elbasvir/grazoprevir	0.019 (6/316)	0.007–0.041	Beta (5.98, 309.02)	3
Elbasvir/grazoprevir with Ribavirin	0.075 (8/106)	0.033–0.143	Beta (7.92, 97.08)	3
Ledipasvir/sofosbuvir	0.048	0.021–0.105	Beta (4.7, 93.2)	27
Ledipasvir/sofosbuvir with Ribavirin	0.085	0.035–0.21	Beta (3.26, 34.97)	27
3D + RBV	0.132	0.055–0.284	Beta (4.29, 28.24)	27
Anti-viral therapy weekly cost				
Elbasvir/grazoprevir	4550			29
Elbasvir/grazoprevir with ribavirin	4921			
Ledipasvir/sofosbuvir	7875			
Ledipasvir/sofosbuvir with Ribavirin	8246			
3D + RBV	5500			
Adverse event cost during treatment				31
Cost of treating depression per episode	2837	2128–3546	Gamma (61.47, 46.16)	
Cost of treating anaemia per episode	4209	3157–5261	Gamma (61.47, 68.48)	

Table 2 | (Continued)

	Base-case	Range	Probability distribution	Reference
Cost of treating rash per episode	475	356–594	Gamma (61.47, 7.73)	
One-time baseline RAVs testing cost	563	422–704		30
Annual health state costs				17, 60, 61
F0–F1	739	555–924	Gamma (61.47, 12.03)	
F2	749	561–936	Gamma (61.47, 12.03)	
F3	1520	1140–1900	Gamma (61.47, 12.18)	
Compensated cirrhosis	1773	1329–2216	Gamma (61.47, 24.72)	
DC	19 695	14 771–24 619	Gamma (61.47, 28.84)	
Post DC	19 695	14 771–24 619	Gamma (61.47, 320.43)	
HCC	36 218	27 163–45 272	Gamma (61.47, 320.43)	
Post HCC	36 218	27 163–45 272	Gamma (61.47, 589.24)	
Liver transplant (first year)	104 730	78 547–130 912	Gamma (61.47, 589.24)	
Liver transplant (subsequent years)	27 484	20 613–34 355	Gamma (61.47, 1703.88)	
Annual discount rate of future cost	3%	0–5%		
Health-related quality of life inputs				
Drug therapy-related multiplier (RBV)	0.85	0.81–0.89	Beta (1537, 0.001)	32
Drug therapy-related multiplier (no RBV)	1.00	0.95–1.05	Gamma (1703, 0.001)	62
F0–F3	0.73/0.86	0.81–0.89	Beta (231.43, 41.21)	63
Compensated cirrhosis	0.69/0.86	0.76–0.84	Beta (302.95, 74.64)	63
DC, post DC	0.65/0.86	0.72–0.79	Beta (374.47, 120.98)	63
HCC, post HCC*	0.65/0.86	0.72–0.79	Beta (374.47, 120.98)	63
First-year, post liver transplant	0.75/0.86	0.83–0.92	Beta (195.67, 28.7)	63
Post SVR, F0–F3	0.75/0.86	0.83–0.92	Beta (195.67, 28.7)	63
Post SVR, F4	0.76/0.86	0.84–0.93	Beta (177.80, 23.39)	63
US population norms, men				64
20–29 years	0.928	0.922–0.934	Beta (6616.65, 513.36)	
30–39 years	0.918	0.912–0.925	Beta (7374.1, 658.69)	
40–49 years	0.887	0.880–0.894	Beta (6970.14, 887.97)	
50–59 years	0.861	0.853–0.870	Beta (6185.19, 998.54)	
60–69 years	0.84	0.827–0.852	Beta (2566.28, 488.82)	
70–79 years	0.802	0.788–0.816	Beta (2496.15, 616.26)	
80–89 years	0.782	0.757–0.807	Beta (819.41, 228.43)	
US population norms, women				64
20–29 years	0.913	0.905–0.920	Beta (4353.04, 414.8)	
30–39 years	0.893	0.886–0.900	Beta (6689.64, 801.56)	
40–49 years	0.863	0.855–0.871	Beta (6124.55, 972.26)	
50–59 years	0.837	0.829–0.846	Beta (6854.42, 1334.85)	
60–69 years	0.811	0.800–0.822	Beta (3946.67, 919.75)	
70–79 years	0.771	0.758–0.784	Beta (3094.35, 919.07)	
80–89 years	0.724	0.701–0.747	Beta (1050.61, 400.51)	

SVR, sustained virological response; F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, numerous septa without cirrhosis; F4, cirrhosis; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; 3D, ombitasvir/paritaprevir/ritonavir and dasabuvir; RBV, ribavirin.

efficacy, unit costs, utility weights, discount rates using the ranges defined in the inputs tables (Table 2).

Probabilistic sensitivity analysis

In order to quantify systematically the impact of overall uncertainty in the estimated values of transition probabilities, sustained virological response rates, costs and utility weights on the ICER of EBR/GZR treatment strategies compared with standard of care, we performed probabilistic sensitivity analysis. Using Monte Carlo simulations methods, we drew 10 000 random samples from pre-defined distributions (Tables 1 and 2).

The parameters of the Gamma and Beta distributions were estimated using the method of moments that relates each parameter to the mean and standard deviation. We used the base-case values as estimates of the mean. Standard errors were estimated from confidence intervals or ranges (Appendix S1).

Results of the probabilistic sensitivity analysis were presented using cost-effectiveness acceptability curves.[35]

This curve summarises uncertainty in the results of the cost-effectiveness analysis by showing the probability a regimen is cost-effective as a function of willingness-to-pay for a QALY gained.

To determine which strategy is cost-effective at a threshold of willingness-to-pay of $50 000/QALY in the one-way sensitivity analysis and probabilistic sensitivity analysis, we calculated the net monetary benefit = (incremental QALYs)*(willingness-to-pay) − incremental costs.

RESULTS

Base-case results

The lifetime cost-effectiveness analysis showed that noncirrhotic treatment-naïve individuals with GT1a who followed an EBR/GZR RAVs testing-based strategy accrued more QALYs than individuals without testing who received EBR/GZR, 3D+RBV, and 8 weeks of LDV/SOF (Table 3). The strategy that included testing also had lower total cost than 3D+RBV or 8 weeks of LDV/SOF. As a result, the RAVs testing-based strategy dominated 3D+RBV or 8 weeks of LDV/SOF and had an ICER of $25 471 compared with EBR/GZR without testing. Although 12 weeks of treatment with LDV/SOF yielded higher QALYs, it produced an ICER of more than $4 million/QALY compared with the EBR/GZR RAVs testing -based strategy (Table 3).

Treatment with EBR/GZR guided by RAVs testing is the most effective regimen among treatment-experienced patients without cirrhosis and cirrhotic patients regardless of prior treatment status. The ICER of this strategy compared with EBR/GZR without testing in treatment-naive or treatment-experienced patients with cirrhosis is $7154/QALY. The ICER in treatment-experienced patients without cirrhosis was $25 471.

Results of subgroup analysis

The results of the subgroup analysis suggest that the ICER of the strategy that included testing compared with EBR/GZR without testing decreased with the severity of fibrosis/cirrhosis (from $57 800/QALY among F0 patients to $7200/QALY among cirrhotic patients). Changing the baseline demographic characteristics from men only to women only had little impact on the results (Figure S1).

Results of sensitivity analyses

Variations of inputs in one-way sensitivity analysis within the range suggested that the results are most sensitive to sustained virological response rates and cost of anti-viral

Table 3 | Total discounted expected costs and QALYs, and the incremental cost-effectiveness ratio associated with each treatment regimen

Patient population and treatment regimen	Total discounted QALYs (years)	Total cost ($)	ICER ($/QALYs)
Treatment naïve patients without cirrhosis			
EBR/GZR + no testing12 weeks	14.1596	59 817	–
3D± RBV 12 weeks	14.1791	75 651	Dominated
LDV/SOF 8 weeks	14.2402	66 599	Dominated
EBR/GZR± RBV + testing	14.2458	62 013	25 471
LDV/SOF 12 weeks	14.2539	96 722	4 303 701
Treatment naïve patients with cirrhosis			
3D± RBV 24 weeks	12.6906	159 245	Dominated
EBR/GZR + no testing 12 weeks	12.7904	73 370	–
LDV/SOF 12 weeks	12.9556	109 651	Dominated
EBR/GZR± RBV + testing	12.9707	74 659	7154
PegIFN/RBV-treatment-experienced without cirrhosis			
EBR/GZR + no testing 12 weeks	14.1596	59 817	–
3D± RBV 12 weeks	14.1930	75 838	Dominated
LDV/SOF 12 weeks	14.2209	97 198	Dominated
EBR/GZR± RBV + testing	14.2458	62 013	25 471
PegIFN/RBV-treatment-experienced with cirrhosis			
3D± RBV 24 weeks	12.7438	158 795	Dominated
EBR/GZR+no testing	12.7904	73 370	–
LDV/SOF+RBV 12 weeks	12.8602	115 507	Dominated
LDV/SOF 24 weeks	12.8765	202 789	Dominated
EBR/GZR± RBV + testing	12.9707	74 660	7153

EBR/GZR, elbasvir/grazoprevir; ICER, incremental cost-effectiveness ratio; LDV/SOF, ledipasvir/sofosbuvir; 3D, ombitasvir/paritaprevir/ritonavir and dasabuvir; RBV, ribavirin; QALY, quality-adjusted life year.

therapy. For example, decreasing the cost of LDV/SOF by 25% resulted in LDV/SOF8 being the only cost-effective option. However, decreasing or increasing the costs of EBR/GZR by 25% did not alter the qualitative results of the base case. Overall, testing-guided treatment of patients without cirrhosis with EBR/GZR was cost-effective at a threshold of willingness-to-pay of $50 000/QALY in 92 of 93 one-way sensitivity analyses (Table S1).

The cost-effectiveness acceptability curves showed that treatment of noncirrhotic treatment-naïve patients with EBR/GZR based on RAVs testing results was cost-effective in 48%, whereas treatment with EBR/GZR irrespective of RAVs status is cost-effective in 40% in all 10 000 simulations at the threshold of $50 000 per QALY (Figure 2). Among this patient population, LDV/SOF8 was cost-effective in 12% whereas OMB/PAR/RIT/DAS± RBV or LDV/SOF12 was not cost-effective in any of the simulations. Retreatment of noncirrhotic patients with EBR/GZR guided by RAVs testing was cost-effective in 55% of the simulations (Figure 3).

Treatment with EBR/GZR based on RAVs testing results was cost-effective in 63% and 85% of the simulations among cirrhotic treatment-naïve and treatment-experienced patients, respectively (Figures 4 and 5).

DISCUSSION

The presence of NS5A RAVs can attenuate the efficacy of new direct-acting antivirals. Testing for RAVs prior to the selecting of the next HCV treatment regimen has the potential to improve efficacy, but adds to cost of therapy. Therefore, it is important to assess the cost-effectiveness of baseline testing for NS5A RAVs in EBR/GZR-treated GT1 patients.

This study showed that RAVs testing-based strategy is superior to 3D+RBV or 8 weeks of LDV/SOF and is cost-effective compared with EBR/GZR without testing. This conclusion is robust in several sensitivity analyses. To our knowledge this is the first study to assess the utility of RAVs testing for guiding HCV treatment with new direct-acting antivirals.

Although this study demonstrated the utility of baseline testing for NS5A RAVs in EBR/GZR-treated patients, RAVs testing has some potential challenges. Currently, the availability of testing for the presence of baseline RAVs varies from place to place, providers are not familiar with the test, and there is no standardised assay for the determination of resistance.

This study had some limitations. First, it excluded the risk of hepatocellular carcinoma even among patients with advanced fibrosis F3. This has the potential of biasing the results against treatment. Second, to simplify the analysis, we did not take into account the fact that patients failing to achieve a sustained virological response may be also retreated with a different regimen. This is unlikely to be a major limitation because only a small percentage of patients fail to achieve a sustained virological response when treated for the first time with

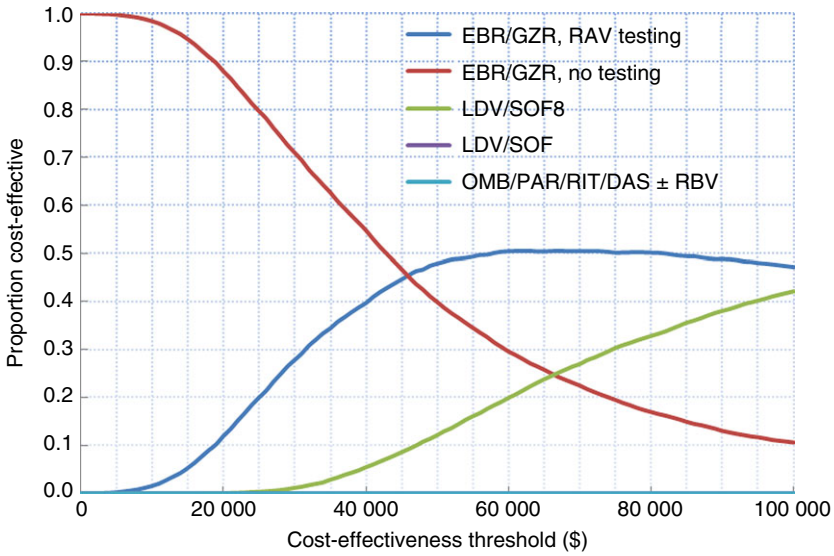

Figure 2 | Cost-effectiveness acceptability curve showing probability of optimal regimen for treatment-naïve patients without cirrhosis among EBR/GZR with RAVs testing, EBR/GZR without testing, LDV/SOF, and 3D for a range of maximum willingness-to-pay for a quality-adjusted life-year (QALY) saved. EBR/GZR, elbasvir/grazoprevir; LDV/SOF, ledipasvir/sofosbuvir; 3D, ombitasvir/paritaprevir/ritonavir and dasabuvir; RBV, ribavirin.

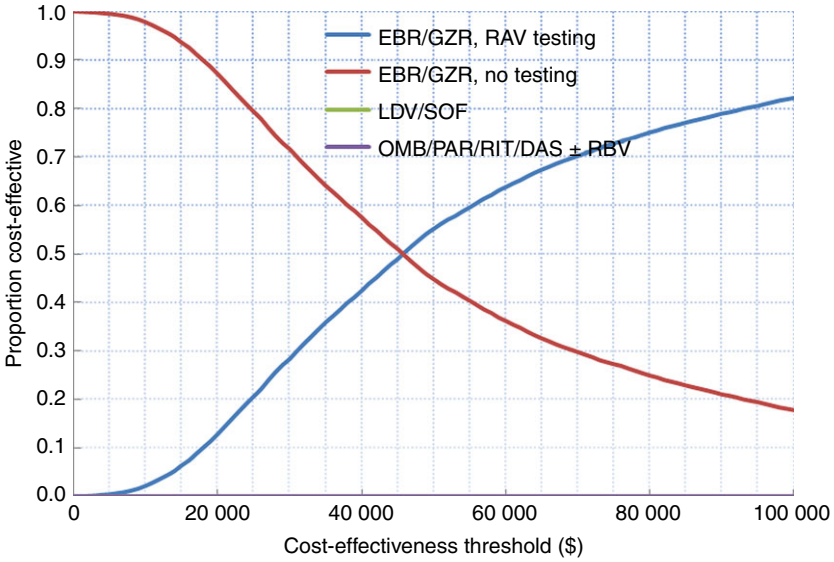

Figure 3 | Cost-effectiveness acceptability curve showing probability of optimal regimen for treatment-experienced patients without cirrhosis among EBR/GZR with RAVs testing, EBR/GZR without testing, LDV/SOF, and 3D for a range of maximum willingness-to-pay for a quality-adjusted life-year (QALY) saved. EBR/GZR, elbasvir/grazoprevir; LDV/SOF, ledipasvir/sofosbuvir; 3D, ombitasvir/paritaprevir/ritonavir and dasabuvir; RBV, ribavirin.

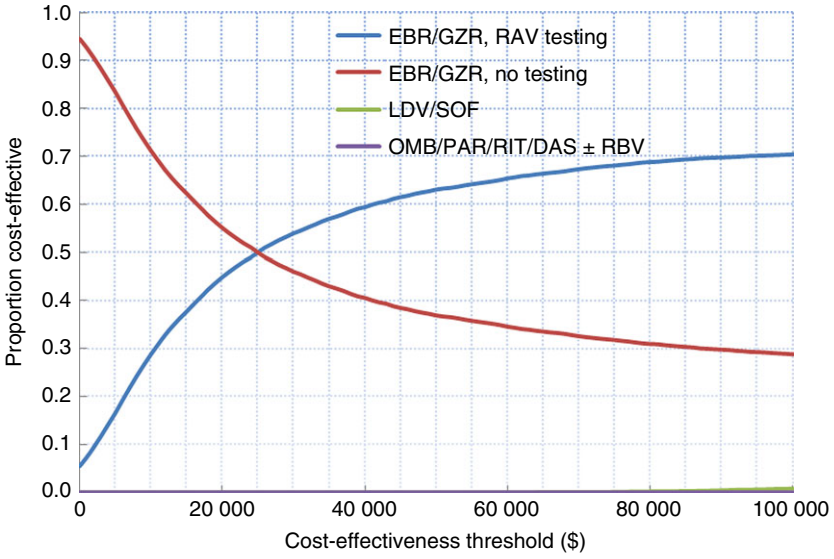

Figure 4 | Cost-effectiveness acceptability curve showing probability of optimal regimen for treatment-naïve patients with cirrhosis among EBR/GZR with RAVs testing, EBR/GZR without testing, LDV/SOF, and 3D for a range of maximum willingness-to-pay for a quality-adjusted life-year (QALY) saved. EBR/GZR, elbasvir/grazoprevir; LDV/SOF, ledipasvir/sofosbuvir; 3D, ombitasvir/paritaprevir/ritonavir and dasabuvir; RBV, ribavirin.

currently available direct-acting antivirals. Third, efficacy inputs were based on data from individual clinical trials with no head-to-head comparative data. Some of these estimates were obtained from *post hoc* analysis which has its own methodological limitations. In addition, conducting *post hoc* analysis created a practical challenge. Among the patients receiving EBR/GZR+RBV for 16 weeks, only a small group of patients harboured NS5A RAVs that reduced the efficacy of the EBR/GZR regimen. As a result, the sample size in the EBR/GZR

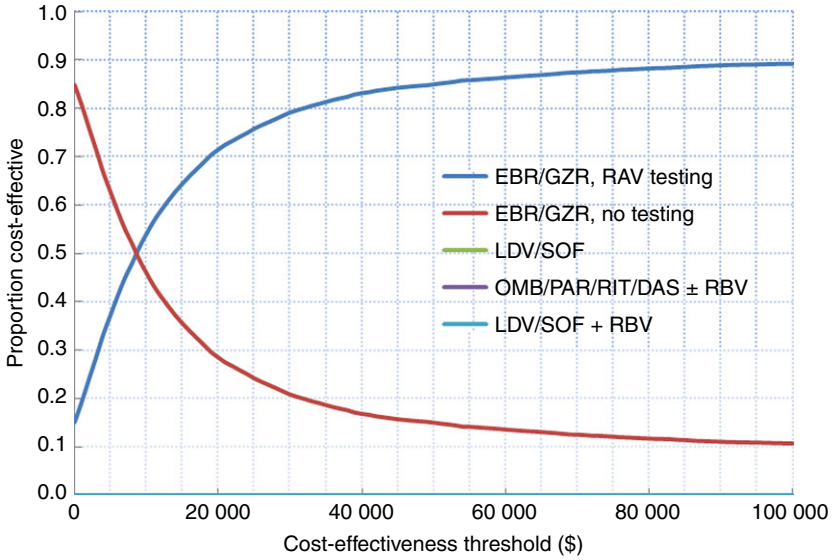

Figure 5 | Cost-effectiveness acceptability curve showing probability of optimal regimen for treatment-experienced patients with cirrhosis among EBR/GZR with RAVs testing, EBR/GZR without testing, LDV/SOF, and 3D for a range of maximum willingness-to-pay for a quality-adjusted life-year (QALY) saved. EBR/GZR, elbasvir/grazoprevir; LDV/SOF, ledipasvir/sofosbuvir; 3D, ombitasvir/paritaprevir/ritonavir and dasabuvir; RBV, ribavirin.

+RBV arm was relatively small (i.e. $n = 6$). This manifested itself in the decision uncertainty regarding RAVs testing, where it was cost-effective in only 48–55% of the simulations of noncirrhotic patients. Fourth, we assumed the efficacy of LDV/SOF and 3D is not affected by RAVs status. There are limited recent data that contradict this assumption.[6, 36] Finally, the study did not consider all regimens currently available to treat GT1a patients, including simeprevir plus sofosbuvir with or without weight-based ribavirin and daclatasvir plus sofosbuvir with or without weight-based ribavirin. This exclusion also covered the very recently launched regimen sofosbuvir/velpatasvir as it was not approved at the time of the analysis.[10]

Despite these limitations our conclusion regarding the cost-effectiveness of EBR/GZR-based regimens in chronic GT1a patients is robust to variation in many model inputs.

Several other modelling studies of cost-effectiveness of treating chronic hepatitis C patients in the USA have shown that treatment with all-oral direct-acting antivirals is a good use of limited healthcare resources.[37] Our results are broadly consistent with those of studies of general HCV patients.

In conclusion, this analysis has demonstrated that RAVs testing before treatment with EBR/GZR is likely to be a cost-effective alternative to the use of EBR/GZR without testing, LDV/SOF, or 3D among GT1a treatment-naïve or treatment experienced patients.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Deterministic one-way sensitivity analysis: net monetary benefit by strategy and input values.

Figure S1. Incremental cost-effectiveness ratio of EBR/GZR with testing vs. no testing by baseline fibrosis/cirrhosis status.

Appendix S1. Choice of distribution for parameters in probabilistic sensitivity analysis.

AUTHORSHIP

Guarantor of the article: Elamin Elbasha.

Author contributions: EE, MR and CN contributed. All authors have contributed to the concept and design, analysis and interpretation of data; and the writing, critical revision and have approved the final version of the manuscript.

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