TITLE: Cost-effectiveness analysis of therapeutic options for chronic hepatitis C genotype 3 infected patients.

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Technical annex.

Additional information describing study design, model's structural framework and parameters included in the deterministic and probabilistic sensitivity analysis.

Cost-effectiveness analysis of therapeutic options for chronic hepatitis C genotype 3 infected patients.

1.- Treatments strategies and effectiveness

Non-cirrhotic patients

EASL guidelines recommended three regimes [1]: SOF/pIFN/RBV for 12 weeks, SOF/RBV for 24 weeks and SOF/DCV for 12 weeks.

On the one hand, efficacy parameters for the SOF/pIFN/RBV and the SOF/RBV combinations were based on the BOSON CT [2], a phase IIIB trial performed to estimate the efficacy and safety of sofosbuvir plus ribavirin, with and without peginterferon-alfa in genotype 2 and 3 patients as follows:

- SOF/pIFN/RBV: pIFN alfa 2a 180 µg weekly plus body weight adjusted RBV and SOF 400 mg once daily for 12 weeks.
- SOF/RBV: body weight adjusted RBV and SOF 400 mg once daily for 24 weeks.

Genotype 3 represented up to 92% of patients included in the CT, with a SVR of 95 and 87 % for SOF/pIFN/RBV and SOF/RBV respectively.

On the other hand, efficacy parameters for the SOF/DCV option were obtained from the phase III ALLY-3 CT[3], trial as follows:

- DCV 60 mg plus SOF 400 mg once-daily for 12 weeks. The SVR reached was 97%.

Given the lack of control group in the cited CTs, the outcomes figures for pIFN/RBV group was obtained from an alternative source [4], with a 74% of SVR.

Cirrhotic patients

EASL guidelines recommended two regimes [1]: SOF/pIFN/RBV for 12 weeks, and SOF/DCV/RBV for 24 weeks.

The BOSON CT provided the evidence for SOF/pIFN/RBV (dosed as in non-cirrhotic) where the achieved SVR was 88%.

In the absence of CTs evaluating the SOF/DCV/RBV 24 weeks option in cirrhotic patients, efficacy parameters were obtained from the European Multicenter Compassionate Use Program in real-life clinical setting, where the achieved SVR was 92% [5].

The SVR rate for pIFN/RBV group was obtained from EPIC CT, with figures of 48% for this subpopulation [6].

Different variables introduced clinical and demographic heterogeneity in CTs populations (fibrosis, age, viral load, race...). However, patients included in CTs where SVR was obtained matched well (**Table I**).

2.- Cost estimations

Drug costs were estimated on the basis of the dosing and therapeutic schemes included in the CTs and SmPC. A perfect adherence was considered on estimations. Cost estimations for pIFN/RBV option took over a 13% of treatment discontinuation at week number 12 due to inadequate response [7]. The costs of the different therapeutic options are shown in the manuscript Table 1.

Monitoring costs. Health care monitoring resource consume was estimated as follows. 12-week course therapy included an initial physician visit, and 4 subsequent visits at weeks 4, 8, 12 and 12 weeks post end-of-treatment. Metabolic and blood cell counts were considered in all 5 visits, and HCV viral load was included at the initial visit and at weeks 4, 12 and post end-of-treatment. 24-week course therapy included 2 additional visits at week 18 and 24 that included metabolic and blood cell counts and a HCV viral load determination at week 24. 48-week course therapy included 3 more additional visits at weeks 32, 40 and 48 that included metabolic and blood cell count determinations. No additional HCV viral load was considered respect to the 24-week course of therapy because the 24 week determination would be transferred to 48 week.

Drug adverse reactions are often associated with an additional cost related to drugs consumption, medical visits, hospital admissions and other resources generated by their treatment. Oral DAA combinations are generally associated with a good tolerance and no additional cost was considered. IFN containing regimens are not as well tolerated, and flu-like symptoms and anemia are the most relevant side effects [4, 6]. The first one could not have relevant direct associated costs, and the second one is often managed with RBV dose reduction. The impact of these side effects on HRQL has been included in associated treatment disutility.

A poorer tolerance to IFN containing regimes is regarded for cirrhotic patients, so an associated side effects cost was considered for this subpopulation with an incidence of 12% neutropenia and 15% anemia [8, 9](**Table II**).

Health care resource costs were obtained from hospitals in the Basque Health Service in 2014. The estimated cost for each disease state is summarized in **Table III**. The transition costs were differentiated from state costs. The former corresponds to the in-hospital care of patients owing to different complications

related to chronic liver disease. The latter includes the cost of resources used in the follow-up [10]. In-hospital care costs for decompensated cirrhosis, hepatocellular carcinoma and liver transplant were obtained from the Basque Country Public Hospitals Statistics Costs System in 2014, based on the patient classification system DRG. Categories corresponding to each liver chronic condition were used for all public hospitals in the Basque Country.

Unit costs were obtained from an ad hoc micro-costing study carried out in all Basque Public Health-Care System hospitals. The costs of in-hospital events were based on the DRG system. Accounting Departments deliver annually resources unit costs and DRGs categories costs for the whole Basque Health Care System. The National Health Care System in Spain share the same funding system for every region in function of the population what means that costs from all regions are similar. These unit costs were checked with those in the Spanish Network of hospital costs (RECH) (<http://www.rechosp.org/rech/faces/es/jsf/index.jsp>) and the results matched well.

3.- Health Related Quality of life - Utilities

Health-state utilities are summarized in **Table IV**. Side effects associated with treatment affect patient's HRQL. Although there were no available data comparing disutility associated with the options evaluated, estimations were performed based on HRQL reduction for dual therapy (pIFN+RBV) published by Grieve *et al.* [11] Good tolerance of IFN-free regimens was considered to have a 50% decrease disutility respect to the SoC. Length of treatment was considered for final estimations in all cases.

4.- Markov model

The model starts at “moderate fibrosis” hepatitis C or “compensated cirrhosis” state where the patient may progress to more advanced disease. Patients in those initial states are susceptible to being treated or not with different antiviral therapeutic alternatives. A SVR from moderate hepatitis, considered the patient to be cured, progressing as the general population. Cirrhotic patients with SVR may evolution to decompensated cirrhosis or HCC at lower transition rates [12, 13]. Mild fibrosis population was not considered in the analysis.

When no SVR is achieved, the disease follows a process with different steps: moderate hepatitis, cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplant and death.

Transition probabilities were obtained from the literature and the revision by Townsend *et al.* [12-19]. Those

probabilities are presented as annual probabilities in the manuscript (to facilitate comparison between studies) and as quarterly probabilities in **Table V**. Given the fast changes that occur during the advanced stages of chronic liver disease, the Markov cycle length was one trimester (3 months), as an annual cycle does not adequately reflect the changes that a patient undergoes. Quarterly probabilities were obtained first by calculating the annual rates and by dividing them by 4 to apply the formula $p = 1 - e^{-r}$ (where p is the probability and r the quarterly rate) [20]. Deterministic probabilities are transformed to quarterly rates by applying the formula $r = -\ln(1-p)/4$ and then converted to quarterly probabilities with the previous formula. The representation of decompensated cirrhosis in cost-effectiveness models varies widely in the literature because of its complex nature. The patient can begin with one or more types of decompensated cirrhosis and become subsequently hospitalized for an alternative form of decompensation. It was followed an approach based on a retrospective study that classified patients into four groups as a function of the first decompensation: ascites, hepatic encephalopathy, gastrointestinal hemorrhage due to portal hypertension and severe bacterial infection[16]. Based on the specific information from each group as a function of the initial decompensation, the re-hospitalization rates for each type of decompensation and death, hepatocellular carcinoma and transplantation rates were calculated. Thus, the structure of the model ensured that each type of decompensation could occur in each group. As a result, the costs as a function of the numbers and types of re-hospitalizations as well as the probability of death can be calculated separately for each group.

The patient could reach hepatocellular carcinoma status from decompensated cirrhosis or cirrhosis. The probability of transition from compensated cirrhosis to hepatocellular carcinoma is 1.4% per annum, according to Fattovich *et al.* [15] Transition probability from decompensated cirrhosis to hepatocellular carcinoma was obtained from Planas *et al.* [16] The annual mortality rate was 42.7% per annum in the hepatocellular carcinoma state [15]. Liver transplantation may be the appropriate treatment for two possible states of the disease, decompensated cirrhosis and hepatocellular carcinoma. Other models do not include this second case, but as 23.9% of all liver transplants performed in Spain in 2010 were for this reason, this transition is justified [18]. Post-transplantation mortality is higher during the first year after transplantation (15% annually) than in subsequent years (3%) [18]. **Table VI** presents the basic figures of events and follow-up by type of initial decompensation obtained from Planas *et al.*, [16] which served to calculate both deterministic probabilities and beta distributions. **Table VII** shows the quarterly probabilities mean values applied in the deterministic models and the alpha and beta parameters used for each transition in the

probabilistic models to calculate the quarterly rates. Those rates were converted to probabilities (p) with the equation $p = 1 - e^{-r}$. The alpha parameter was the number of events for each transition and the beta was the follow-up time in quarterly minus the number of events because the mean rate is $\alpha/(\alpha+\beta)$.

5.- Base case results

Two figures have been included in the Technical Annex to represent the results of the base case in moderate fibrosis and cirrhotic patients (**Figure I and II**).

6.- Probabilistic sensitivity analyses

This approach is based on randomly varying all the parameters within a distribution range at the same time in each Monte Carlo simulation. This enables the examination of the effect of uncertainty in the model's variables. The advantages include the ability to provide global analysis of variability and new interpretative tools, such as the cost-effectiveness plane, acceptability curves, and the expected value of perfect information [21-24].

A distribution is attached to the range associated with each of the parameters in the analysis and a random generator selects values from the specified distribution. This allows the examination of the effect of joint uncertainty in the variables of the model. The model was run 1,000 times calculating the difference in cost (incremental cost) and effectiveness (incremental effectiveness) between both alternatives on each run. The results of the PSA are presented as a “cost-effectiveness” plane that displays graphically the variability between costs and effectiveness. Vertical axis represents the incremental cost of each simulation and horizontal axis the incremental effectiveness. The result of each run is plotted in the plane to produce a cloud of points [25]. The National Institute for Clinical Excellence (NICE) has acknowledged this method as the appropriate approach to reflect uncertainty in cost-effectiveness studies [26].

A report by Wright *et al.* described the distributions applied to the probabilistic sensitivity analysis, using beta functions for “probabilities” and “utilities”, and gamma for “costs” [23]. Additionally, following the recommendations of Briggs *et al.*, both gamma and lognormal functions can be applied to “costs” [21].

Beta distributions parameters were calculated based on the confidence intervals obtained from the literature. Beta distribution is the appropriate function for probabilities given its range from zero to one. Its parameters are alpha and beta and the mean is calculated as $\alpha/(\alpha+\beta)$. Minimum and maximum figures described by Townsend *et al.* were used as an approximation of 95% confidence intervals when they were

not available. Therefore, the beta functions were estimated with the adequate quarterly mean and 95% confidence intervals.

The availability of patient-level data for “transition costs” allows applying a log-normal distribution and the inclusion of the information in the probabilistic sensitivity analysis (**Table VIII**). The cost of follow-up was based on the expert advice regarding resource consumption and the unit resource cost from Basque hospitals. Estimations were based on previous analysis [8]. Resources consumption and unit costs are shown in **Table III**.

“Utilities” were introduced as beta distributions (**Table IV**). The parameters for different beta distributions were calculated based on the confidence intervals from the literature[11].

Probabilistic sensitivity analysis results are shown in manuscript figures 2 and 3 for “base-case” cost-effective options (SOF/pIFN/RBV for 12 weeks either in “moderate fibrosis” or “cirrhotic” patients). **Figures III and IV** in the Technical Annex, show the results for “base-case” non-cost-effective options at official prices (IFN free regimes for both “moderate fibrosis” and “cirrhotic” patients).

7.- Model validation

Estimations of life expectancy in different health states of hepatitis C were made to validate the model. Both “life expectancies” from different states and the percentage of patients who progress to cirrhosis (21% at 20 years and 37.4% at 30 years) were calculated (**Table IX**). Those were similar to other models’ results [17]. Hepatic mortality (advanced liver disease, liver transplant, and liver related mortality) was separately calculated from other-cause mortality in a 49-years-old chronic hepatitis C patients’ cohort. Liver-related mortality accounted for 24% of total mortality.

SVR patients’ survival was similar to that of the general population. As expected, early stage chronic hepatitis C patients die from other causes and when decompensated cirrhosis stage is reached, death occurs due to liver disease complications.

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9.- Tables

Table I. Demographics and baseline characteristics of CTs populations included in the analysis.

Non cirrhotics*	REFERENCE	GENOTYPE 3 (N)	AGE (median)	MALES (%)	RACE % (W/AS/AA)	log mean HCV-RNA	F0,F1,F2,F 3 (%)	F4 (%)
SOF/DCV x 12 weeks	[3]	101	53	57	91 / 5 / 4	<800,000 = 31% >800,000 = 69%	75	22
SOF/pIFN/RBV x 12 weeks	[2]	181	50	67	84 / 13 / 1	6,3 (0,69)	68	32
SOF/RBVx 24 weeks	[2]	182	49	65	84 / 13 / 1	6,2 (0,71)	69	31
RBV/pIFN x 24 weeks	[4]	176	48	64	87 / 6 / 2	6,0 (0,8)	79	21
Cirrhotics*	REFERENCE	GENOTYPE 3 (N)	AGE (median)	MALES (%)	RACE % (W/AS/AA)	log mean HCV-RNA	F0,F1,F2,F 3 (%)	F4 (%)
SOF/DCV/RBV x 24 weeks	[5]	39	56	70	91 / 4 / 2	6.02 (1.04- 7.16)	8	81
SOF/pIFN/RBV x 12 weeks	[2]	181	50	67	84 / 13 / 1	6,3 (0,69)	68	32
RBV/pIFN x 48 weeks	[6]	122	50.5	71	84 W	≤600,000 = 38% >600,000 = 61%	0	100

W: White; AA: African American; AS: Asian.

*: SVR for cirrhotic and non-cirrhotic was estimated according to the patients included in CTs for each fibrosis stage.

Table II. Side effects' cost estimations.

ANEMIA
<ul style="list-style-type: none"> • 2 physician visits • 2 laboratory tests • 15 % patients considered appropriate candidates for treatment with erythropoiesis-stimulating agents (epoetin alfa: dose of 40.000 UI / week).
NEUTROPENIA
<ul style="list-style-type: none"> • 2 physician visits • 2 laboratory tests • 20 % patient considered appropriate candidates for treatment with filgrastim (dose of 300 µg/week).
Estimations are based on previous analysis (Blazquez <i>et al.</i>)[8]

Table III. Follow-up costs (unit costs obtained from the Basque Public Hospitals accounting system 2014 and expert advice regarding resources consumption)

Disaggregated cost	Total cost (€)	Consultation	Lab tests	Echography	Endoscopy	Paracentesis	CT	In-hospital stay
Unit cost (€)		81.4	30	49.5	76.2	120.0	173.1	3,720.4
Mild hepatitis C	272	2	2	1				
Moderate hepatitis C	272	2	2	1				
Compensated cirrhosis	398	2	2	2	1			
Ascites	1,288	10	10	2	1	10		
GHPH	1,465	6	6	2	6	2		
Encephalopathy	518	2	2	2	1	1		
Bacterial infection	398	2	2	2	1			
HCC	4,734	4	4	4	1	1	1	1
Liver transplantation year 1	4,945	11	11	0	0	0	0	1
Liver transplantation year 2	4,166	4	4					1

CT: Computerized tomography; GHPH: gastrointestinal hemorrhage due to portal hypertension. HCC: hepatocellular carcinoma; Lab test: Laboratory test

Table IV. Markov model utility values and probabilistic parameters for states associated with hepatitis C (obtained from Grieve et al.) [11].

State	Average utility	Distribution	Parameter alpha	Parameter beta
Mild hepatitis	0.77	Beta	480	143.38
SVR mild hepatitis	0.82	Beta	55	12.07
Moderate hepatitis	0.66	Beta	165	90.15
SVR moderate hepatitis	0.77	Beta	130	38.8
Cirrhosis	0.55	Beta	50	40.91
SVR cirrhosis	0.61	Beta	110	64
Decompensated cirrhosis	0.45	Beta	110	134.44
HCC	0.45	Beta	110	134.44
Liver transplant	0.45	Beta	110	134.44

HCC: hepatocellular carcinoma; SVR: sustained viral response.

Table V. Markov model probabilistic parameters for quarterly transitions between chronic hepatic C disease states

State		Quarterly probability			Beta distribution		Source References
From	to	Mean	LowerCI	UpperCI	alfa	beta	
Mild Hepatitis C	Moderate Hepatitis C	0.00938	0.00486	0.01535	12	1,267	[27]
Moderate Hepatitis C	Compensated cirrhosis	0.01300	0.00826	0.01878	23	1,746	[27]
Compensated cirrhosis	Decompensated cirrhosis	0.01015	0.00585	0.01690	14	1,365	[16]
	HCC	0.00352					[16]
HCC	Death	0.12996	0.10489	0.15973	76	504	[16]
HCC: hepatocellular carcinoma.							

Table VI. Number of events of decompensated cirrhosis stages associated with hepatitis C (raw data obtained from Planas et al.)[16].

	Group separated by initial decompensation				All
	Ascites	Encephalopathy	GHPH	Infections	
Patients; N	96	10	65	29	200
Follow-up; patient-trimesters	1,002.32	64.32	900.68	297.2	2,264.52
Ascites	102	3	33	21	159
Encephalopathy	61	21	101	11	194
GHPH	8	0	55	3	66
Infections	40	9	25	22	96
HCC	18	0	12	3	33
Transplantation	1	0	1	1	5
Death	35	6	12	10	63
GHPH: gastrointestinal hemorrhage due to portal hypertension. HCC: hepatocellular carcinoma					

Table VII. Average quarterly probabilities and probabilistic parameters for quarterly transitions rates among decompensated cirrhosis stages associated with hepatitis C (from Planas et al.) [16]

From ascites to	Average Quarterly Probability	Rate Parameter alpha	Rate Parameter beta
Ascites	0.092	102	900.32
Encephalopathy	0.057	61	941.32
GHPH	0.008	8	994.32
Infections	0.038	40	962.32
HCC	0.018	18	984.32
Transplantation	0.001	1	1,001.32
Death	0.034	35	967.32
From encephalopathy to	Average rate	alfa	beta
Ascites	0.045	3	61.32
Encephalopathy	0.246	21	43.32
GHPH	0.000	0	64.32
Infections	0.123	9	55.32
HCC	0.000	0	64.32
Transplantation	0.000	0	64.32
Death	0.085	6	58.32
From GHPH to	Average rate	alfa	beta
Ascites	0.035	33	867.68
Encephalopathy	0.101	101	799.68
GHPH	0.058	55	845.68
Infections	0.027	25	875.68
HCC	0.013	12	888.68
Transplantation	0.001	1	899.68
Death	0.013	12	888.68
From infections to	Average rate	alfa	beta
Ascites	0.066	21	276.2
Encephalopathy	0.036	11	286.2
GHPH	0.010	3	294.2
Infections	0.069	22	275.2
HCC	0.010	3	294.2
Transplantation	0.003	1	296.2
Death	0.033	10	287.2
GHPH: gastrointestinal hemorrhage due to hypertension. HCC: hepatocellular carcinoma			

Table VIII. Estimated CHC state transition costs (from the Basque Public Hospitals accounting system 2014).

	Number of patients	Distribution	Mean Ln cost (€)	Standard deviation Ln cost (€)
Ascites	618	Lognormal	7.823	0.106
Encephalopathy	681	Lognormal	9.002	0.337
GHPH	433	Lognormal	7.817	0.106
Infections	623	Lognormal	8.061	0.654
HCC	136	Lognormal	10.122	0.889
Liver transplant	50	Lognormal	11.625	1.164
CHC: Chronic hepatitis C; GHPH: gastrointestinal hemorrhage due to hypertension				

Table IX. Chronic liver disease stage and general population life expectancies by age. Model validation.

Age	General population	Sustained Viral Response	Mild Hepatitis C	Cirrhosis	Decompensated Cirrhosis
40	43.36	42.67	39.61	23.47	8.99
50	34.22	33.34	32.08	21.36	8.84
60	25.13	24.59	24.23	18.38	8.56
70	17.07	16.52	16.49	14.33	7.99

10.- Figures.

Figure I. Cost-effectiveness of therapeutic options considered in the analysis for moderate fibrosis patients.

Figure II. Cost-effectiveness of therapeutic options considered in the analysis for cirrhotic patients.

Figure III. Base-case “Cost-effectiveness” plane and “acceptability curve” for “SOF/DCVx12w” vs “pIFN/RBVx24w” in moderate fibrosis patients (a 40% reduction in drug acquisition costs was also drawn in the acceptability curve).

SOF_DCV: SOF+DCV for 12 weeks

SOF_DCV_DISCOUNT: SOF+DCV for 12 weeks with a drug acquisition cost reduction of 40%

Figure IV. Base-case “Cost-effectiveness” plane and “acceptability curve” for “SOF/DCV/RBVx24w” vs “pIFN/RBVx48w” in cirrhotic patients (a 40% discount in drug acquisition costs capped to 12 weeks was also drawn in the acceptability curve).

SOF_DCV_RBV: SOF+DCV+RBV for 24 weeks
SOF_DCV_DISCOUNT: SOF+DCV+RBV for 24 weeks with a drug acquisition cost reduction of 40% and capped to 12 weeks