Mrs S, 63 years old, admission for ascites

- Diabetes, past history of hypertension, no alcohol intake
- HCV cirrhosis in 2011 (G 1)
- 2007: IFN + Ribavirine, stopped at M4 (Platelets 23 000/mm3)
- Ascites for 8 months (6-8 L/week), 2 episodes of overt encephalopathy (urinary tract infection)

- Physical examination:
  - 1.64m, 73 kg
  - Flapping
  - Tense ascites, umbilical hernia
  - Poor nutritional status

Lab tests and imaging

- **Biology**
  - AST 1.5 N; ALT 1.2 N; GGT 1.5 N; ALP N, Total bilirubin 60 µmol/L
  - Na 126 mmol/L, Creatinine 90 µmol/L, Albumine : 22 g/L
  - INR 1.6, Platelets count: 54 000/ mm3
  - Child C11, MELD 17

- **Endoscopy:** oesophageal varices grade I

Which therapeutic option for ascites?

- Diuretics
- Iterative ponctions
- TIPS
- Other conservative option
- Liver Transplantation

Refractory ascites: therapeutic options

Treatment	Advantages	Disavantages
Paracentesis	Easy, effective No contra-indication	Frequently repeated bleeding, leakage, strangulation, PICD Palliative
TIPS	Effective (75%) Improvement of renal function, nutritional status, QOL	Failure, bleeding, encephalopathy Contra-indication: encephalopathy, liver insufficiency (MELD > 18) Palliative
AlfaPump®	Preliminary data	
LT	Definitive	Morbidity, mortality

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Which therapeutic option for ascites?

- Diuretics: no (hyponatremia)
- Iterative ponctions (palliative option)
- TIPS (encephalopathy, MELD 17)
- Other (no validation)
- **Liver Transplantation**

Pretransplant evaluation

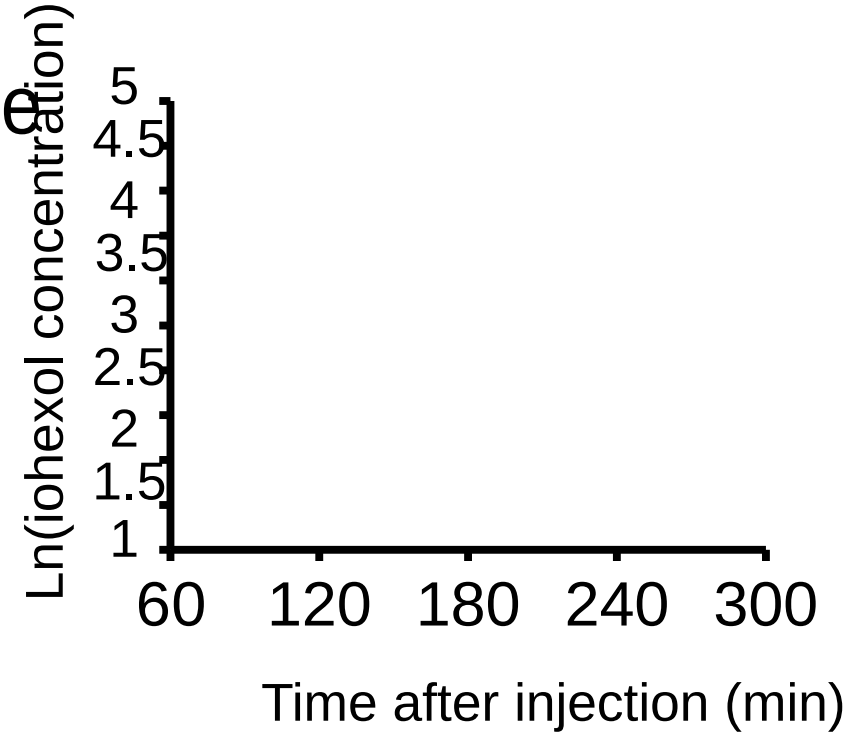
- Imaging: no HCC, no vascular abnormalities
- Cardiopulmonary evaluation
  - Normal lung CT-scan
  - Echocardiography: preserved ejection function, no systolic pulmonary hypertension
- Kidney evaluation
  - Normal urinary sediment, no proteinuria
  - Normal imaging

What about Renal Function?

- Normal renal function
- Other kidney evaluation is needed
- Renal dysfunction

Evaluation of GFR in cirrhosis

- Exogenous agent clearance (iohexol, iothalamate)
- Time-consuming
- Costly
- Difficult to use in routine



Clearance = Dose / AUC

Francoz et al. Liver Transplantation 2010;16:1169-1177

Evaluation of renal function in cirrhosis

- Creatinine: poor marker of renal function

Equation	Calculated GFR – measured GFR*
Cockcroft	+ 25 mL/min
MDRD-4	+ 16 mL/min
CKD-EPI	+ 9 mL/min

If LT is considered : equation that underestimates to avoid overlooking severe renal disease (CLKT?)

What about Renal Function?

- Normal renal function
- Other kidney evaluation is needed
- Renal dysfunction
  - MDRD-4: 55 mL/min/1.73 m2
  - MDRD-6: 27 mL/min/1.73 m2
  - GFR (Iohexol clearance): 28 ml/min/1.73 m2
  - Kidney biopsy
    - 20% glomerulosclerosis
    - 10% interstitial fibrosis
    - No other lesion

PreLT evaluation

- No contra indication
- No need of kidney transplantation (GFR 28 mL/min but no criteria for CKLT)
- MELD 17, refractory ascites

Listed for LT alone

HCV treatment

- Treatment is not recommended because there is an indication for LT
- Treatment is not recommended because of decompensated cirrhosis
- The aim is to improve liver function and to delisting
- PreLT treatment is aimed preventing reinfection of the graft
- HCV treatment will be efficace and well tolerated after LT

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HCV treatment before LT

There is an on-going debate as to whether patients with decompensated cirrhosis on the transplant list should be treated for their HCV infection prior to liver transplantation or, conversely, transplanted first and treated promptly after transplantation. Thus far, no consensus has been reached because these two approaches have not been prospectively compared in appropriately powered randomized trials using clinical endpoints. **CPG EASL 2016, Treatment of HCV**

- Aims
  - Prevention of liver graft infection after transplantation
  - Improvement of liver function before transplantation, delisting of some patients

SVR in decompensated cirrhosis, main studies

OLAR [77, 78]	LDV/SOF ± RBV	12-24	140	57-89%	54	5
LLY-1 [76]	SOF + DCV + RBV	12	60	56-94%	14	3
UP [80]	SOF + DCV or SOF + LDV	12	467	81.6% (68.8-90.9%)	89	15

- SVR: 50-100% (much higher than with IFN-based!)
- Disease not so severe (MELD<20)

van den Meer, Berenguer. Journal of Hepatology 2016 vol. 65 j S95–S108

SVR in decompensated cirrhosis, changes in liver function with DAA

Number of patients evaluated	93	81	39	250
Time at evaluation	SVR-4	SVR-24	SVR-12	SVR-12
MELD changes				
Improvement	67%	73%	40%	54%
In CTP-B cirrhosis	64%	65%	43%	54%
In CTP-C cirrhosis	70%	83%	67%	-
Worsening	17%	16%	40%	25%
In CTP-B cirrhosis	17%	20%	43%	25%
In CTP-C cirrhosis	18%	11%	0%	-
CTP changes				
Improvement	67%	77%	76%	47%

- MELD, CTP improvement: 40-80%
- MELD, CTP worsening: 10-20%
- Whatever the severity of cirrhosis

van den Meer, Berenguer. Journal of Hepatology 2016 vol. 65 j S95–S108

Delisting

- 3 studies (*Belli et al, J Hepatol 2016;65:719-26. Coilly et al;Abstract AASLD 2015, Pascasio et al; abstract ILC 2016*)
- Delisting rate due to clinical improvement: 15 to 20% of patients
- Higher probability when MELD<16 (30%), low when MELD>20 (5%)
- Other predictive factors for delisting?

- Unresolved issues
  - How long clinical improvement?
  - What about the risk of HCC?

Mrs S: therapeutic options?

- Sofosbuvir + Ledipasvir
- Sofosbuvir + Daclatasvir
- 3D
- Grazoprevir/ elbasvir

Mrs S: therapeutic options?

- Sofosbuvir + Ledipasvir CI, GFR< 30 mL
- Sofosbuvir + Daclatasvir
- 3D
- Grazoprevir/ elbasvir

Mrs S: therapeutic options?

- Sofosbuvir + Ledipasvir
- Sofosbuvir + Daclatasvir
- 3D
- Grazoprevir/ elbasvir

CI, decompensation (PI)

Mrs S: listed, no HCV treatment

- LT after 8 months (Refractory ascites: MELD exception in France, delay of about 6 months after listing)
- LT, post operative period without any complication, tacrolimus, MMF and steroids
- Treatment 1 year after LT (fibrosis F1): Sof+Ledi+Riba (3 months Screat: 65 µM, MDRD4 70 mL/min), SVR achieved

Take Home Messages: to treat or not to treat before LT?

- Improvement of liver function and delisting after HCV eradication is possible in patients with decompensated cirrhosis (20%? 30%?)
- Worsening is observed in 10 to 20%
- The highest probability of delisting mainly concern patients with MELD score<16
- In patients with MELD score>20, this probability is very low (No DAA? postLT treatment?)
- There are still unresolved issues: (1) factors predicting evolution of liver function after virosuppression, (2) risk of HCC?

Take Home Messages: which DAA regimen?

- Protease inhibitors are definitely contraindicated in decompensated cirrhosis

- Sofosbuvir must be avoided in patients with GFR<30 mL/min

- Since current renal evaluation often fail to detect severe kidney disease in patients with the most severe forms of cirrhosis, a true GFR (exogenous clearance) must be performed before using Sofosbuvir or ribavirin