Management of hepatitis C in transplanted patients

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Case

- M. S, 59 years old

- History of HCV:
  – Transfusional contamination in 1982
  – Diagnosis of HCV related cirrhosis in 2004 after a first decompensation in a context of acute prostatitis
  – Genotype 1b, IL-28B polymorphism CT (*a posteriori*)
  – In 2005, treatment with PEG-IFN-α2a and RBV, moderately tolerated (anemia, asthenia): Stop because of non-response (W12)

- History of liver transplantation
  – In 2005-2006, 25 MELD, ascites, Child-Pugh C10
  – Orthotopic liver transplantation in April 2006 (Donor 64 years)
  – Immunosuppression: steroids (stop 6 months post-LT), mycophenolate mofetil and cyclosporine

Case

History of HCV recurrence:

- Protocol biopsies
- At 1 year: A3F1 lobular hepatitis
- At 2 years: A1F2 lobular hepatitis

  Therapy with PEG-IFN α-2a 180 mcg/wk + RBV 1000 mg/day (weight 74 kg)

  Anemia treated with EPO

  Detectable viral load at W24. Stop treatment

In October 2010 (4 years post LT)

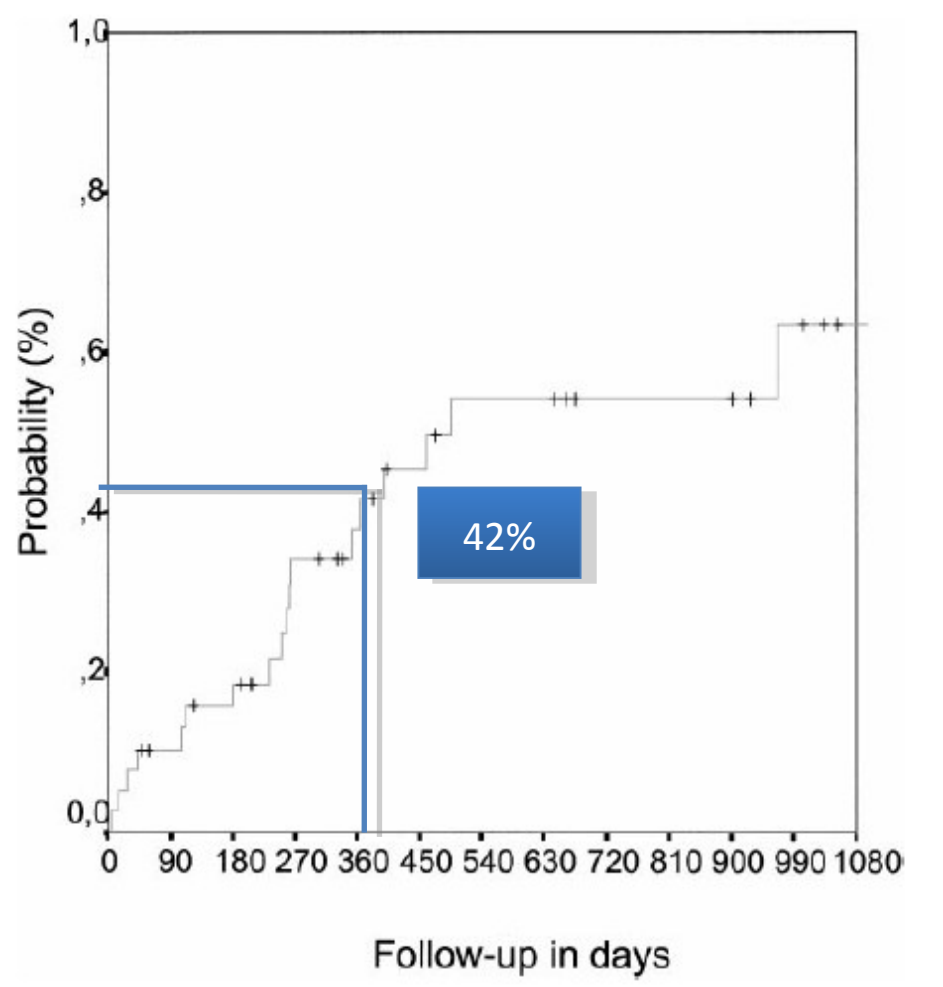
- Weight 76 kg, clinically stable, no ascites, no encephalopathy
- Neoral 225 mg/day
- Liver stiffness: 16kPa
- Liver biopsy: A1F4. No rejection. No steatosis
- PT 92%, INR1.1, Total Bilirubin 32 mcmol/L, AST 126 IU/L, ALT 80 IU/L
- Hb 12.6 g/dL, neutrophils count 3,450 G/L, Platelets 120 G/L
- GFR 65 mL/min

Question

What are the correct answers?

1. The 3-months mortality is around 50%
2. The risk of decompensation is 40% at 1 year
3. HCV antiviral therapy is required

HCV recurrence



- **20 to 30% graft cirrhosis** after 5 years
- Responsible for 2/3 of graft loss
- Probability of decompensation **of 42% at 12 months**

Berenguer M, Hepatology, 2000

Case

What do you propose?

1. Peg-IFN + RBV therapy
2. Triple therapy based on a 1st generation Protease Inhibitors (PI)
3. I postpone the treatment until we have access to an IFN free regimen post-transplantation

Treatment of recurrence after LT

Efficacy of Peg-INF + RBV in LT recipients

	n	Type study	D/C (%)	SVR (%)
Neff	57	R,U	31	14
Berenguer	36	R, U	47	50
Oton	55	P,U	29	44
Mukherjee	39	R,U	43	33
Fernandez	47	P,U	21	23
Picciotto	61	P,U	15	28
Angelico	42	P,C	33	33
Carrión	54	P,C	39	33

SVR: About 30%

R: retrospective; U: uncontrolled; P: prospective; C: controlled; D/C: discontinued therapy

→ SVR after transplantation increases patient and graft survival

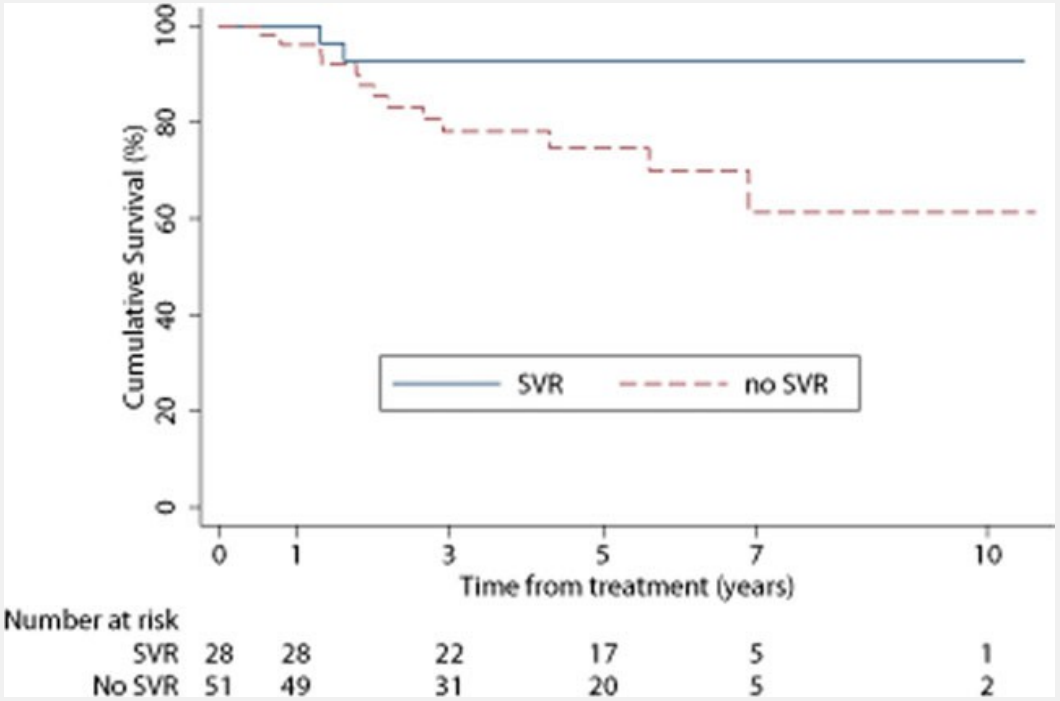
Roche, Liver Transplantation, 2008

Treatment of recurrence after LT

Efficacy of retreatment with Peg-INF + RBV in LT recipients

- 301 patients (four centers, 87% G1)
- SVR 35% (25% F3-F4)

Patient survival since retreatment

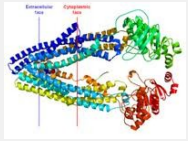


Berenguer M. Liver Transpl. 2012

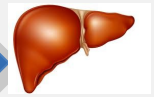
2nd option : Triple therapy

- **Problems of drug interactions**

Move the substrate
(P-glycoprotein)



Protease inhibitors
Calcineurin inhibitors



Inhibit the hepatic
metabolism (CYP3A4)

- **Three initial series** have been published over the last years showing
  - Feasibility in managing **drug-drug interactions**

	Boceprevir	Telaprevir
Tacrolimus	x5	**x30**
Cyclosporine	x2	**x3**

- **Encouraging results** in terms of efficacy in interim analysis

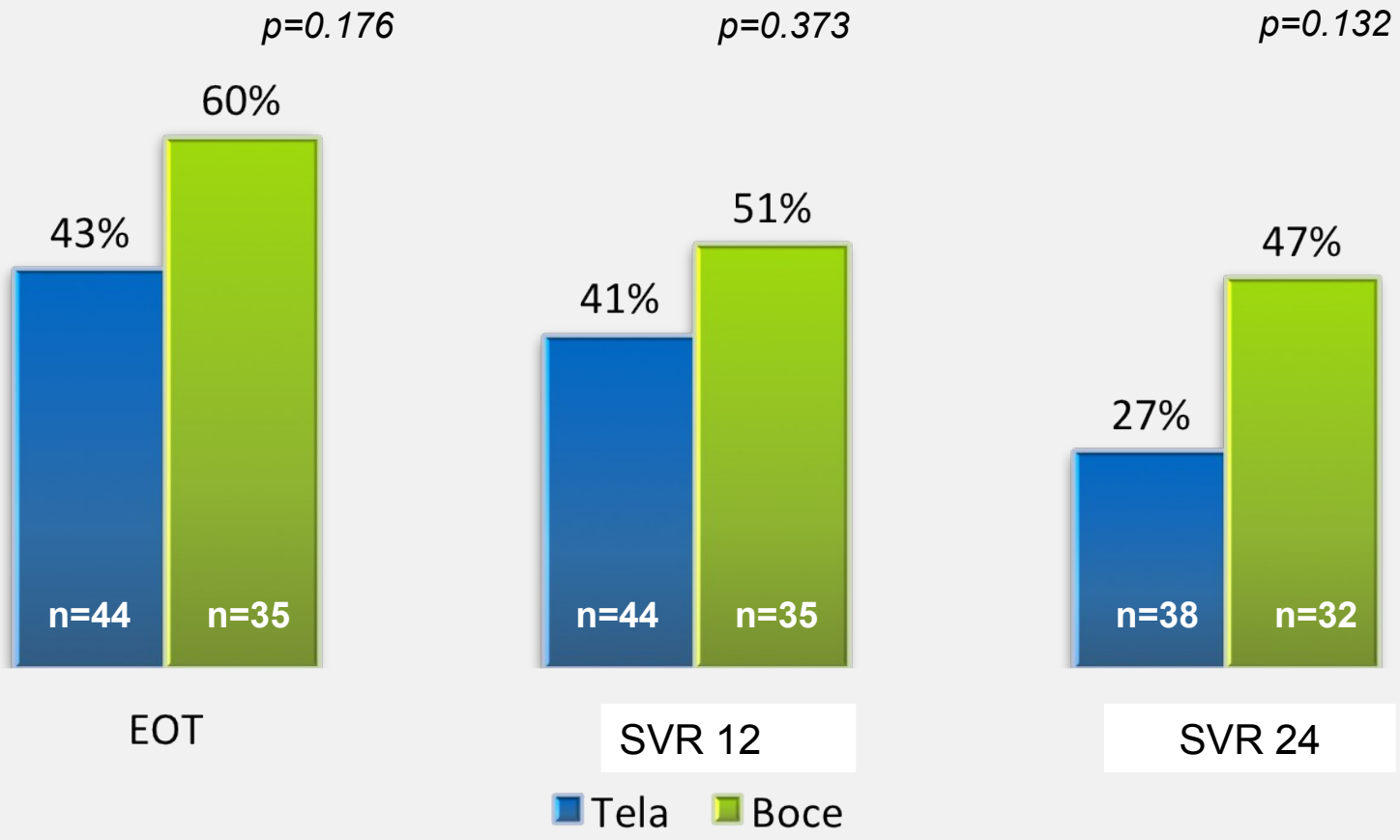
Coilly, AAC, 2012, Werner, Liver Transpl, 2012, Pungpapong, Liver Transpl, 2013

Triple therapy: The french experience

- **Study cohort** (in 17 liver transplant centers)
- **N=79** (who have achieved SVR12)
- Genotype 1 active and chronic hepatitis C (68% G1b)
- Recurrence defined by a fibrosis stage >1 (METAVIR) or FCH
- Stable immunosuppressive regimen and no HBV or HIV coinfection (cyclosporine: 52%)
- Indication of triple therapy

	Boceprevir (n=35)	Telaprevir (n=44)	*p*
Baseline MELD score	11.0 ± 4.5	11.2 ± 6.8	ns
Fibrosis stage (METAVIR) – (%) ≥ F3 F4	 39% 24%	 48% 23%	ns
FCH	6%	16%	ns

Triple therapy after LT: efficacy



** Undetectable viral load; in intention-to-treat*

Coilly AASLD 2013

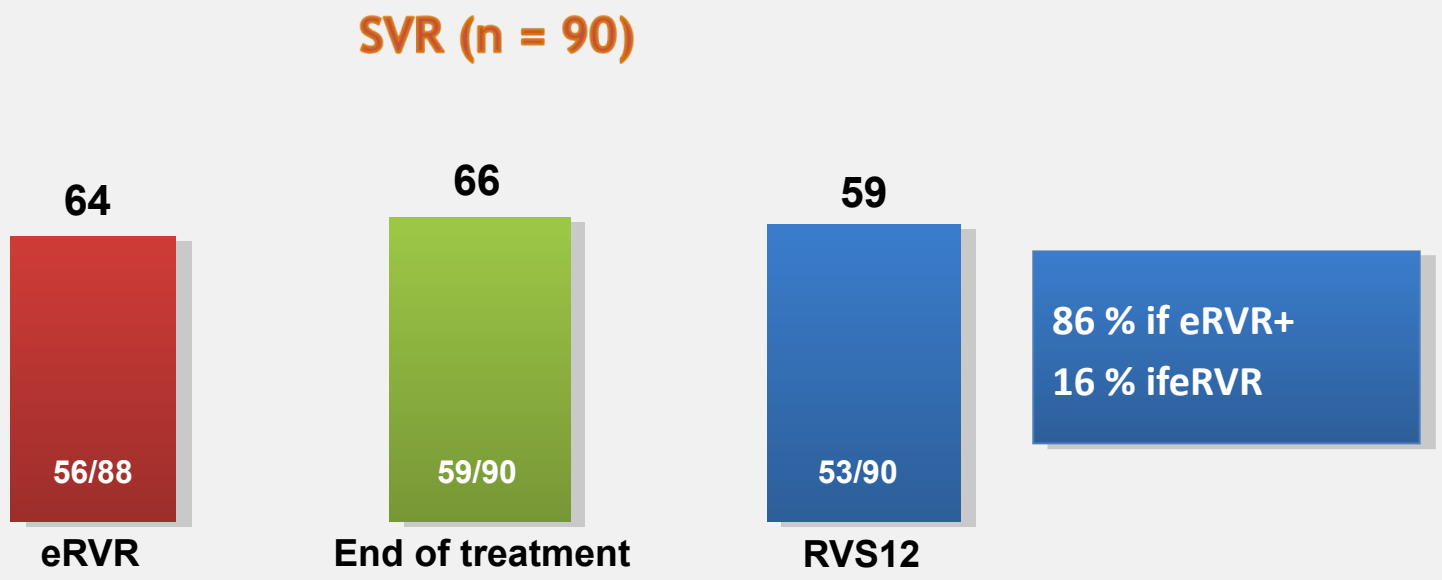
Predictive factors of SVR 12

		Univariate (p)	Multivariate (p/OR/95% CI)	
Before treatment				
Host	IL28B CC status	0.119		
	BMI<25	0.026		
	Non response to dual therapy	0.106	0.059	
Baseline	Bilirubinemia	0.052		
	Albuminemia	0.021		
	Creatinine clearance	0.021		
IS	**Ciclosporine use**	**0.024**	**0.0049**	**5.0 [1.6-15.5]**
	No steroids at baseline	**0.067**	**0.0083**	**6.3 [1.6-25.8]**
During treatment				
EVR		**<0.00001**	**0.0004**	**46 [5-386]**
Baseline RBV dose		0.003	0.0543	
Treatment duration		<0.0001		

Coilly AASLD 2013

The CRUSH-C cohort

- 125 patients after liver transplantation, median age: 58 years, males: 75%, cyclosporine: 58%
- G1a: 58%, F3 / 4 (48%), treatment failure with PR post-LT: 47%, Interval between LT and treatment: 3.4 years



- Reduction of PEG-IFN doses = 38 %
- Reduction of ribavirin doses = 86 %

Stravitz RT, AASLD 2013

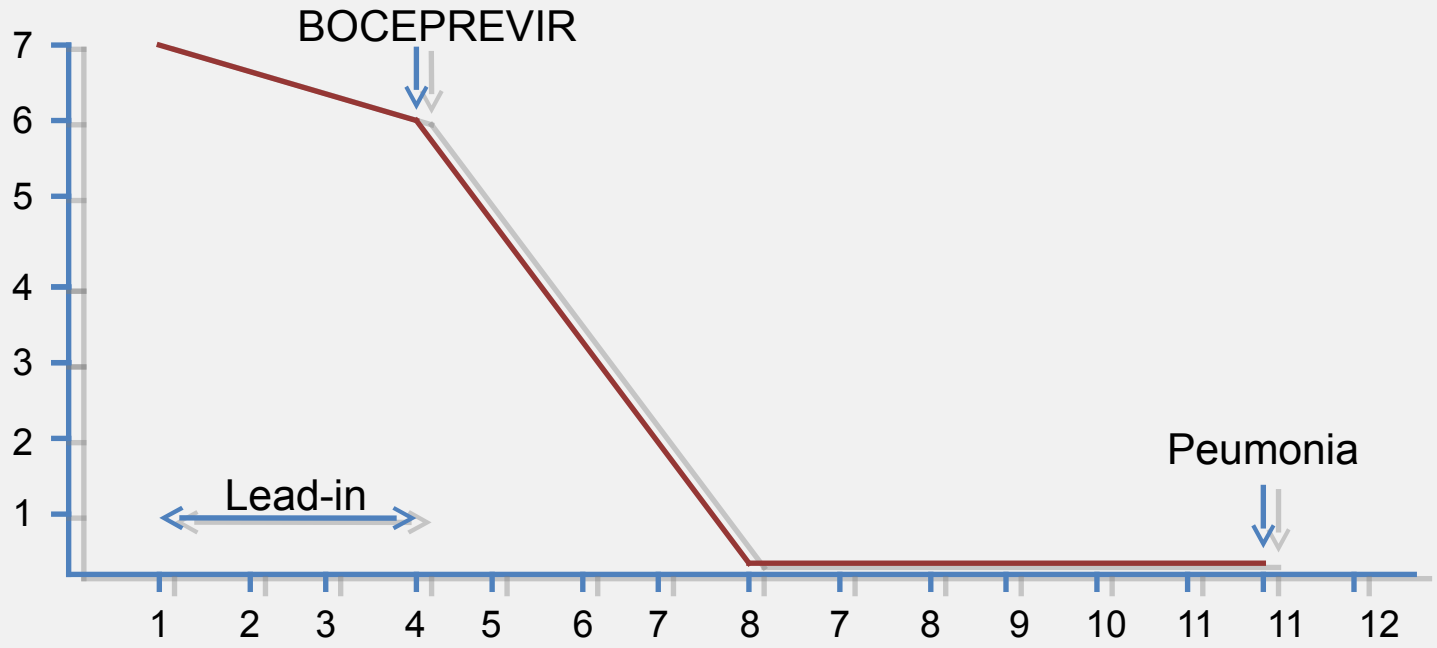
Case

Triple therapy with Peg-IFN + Riba + Boceprevir

Undetectable viral load (W8)

Platelets 80 G/L, neutrophils 1,050 G/L

Stable hemoglobin level about 10 g/dL with EPO and without ribavirin dose reduction



At week 11, hospitalization for fever, cough and dyspnea due to a severe pneumonia

Question

Do you discontinue treatment?

1. No, HCV RNA is undetectable, we have to purchase

2. No, not absolutely required without sign of decompensation

3. Yes, because of severity of the infection

Discontinuation and failure

	BOCEPREVIR	TELAPREVIR
Premature discontinuation (n/%)	17 (48%)	27 (61%)
Discontinuation for AE (n/%)	7 (20%)	14 (32%)
Other reasons (n)	1 HCC recurrence	1 reLT
Treatment failure during treatment		
Partial response (n/%)	5 (14%)	6 (14%)
Null response (n/%)	1 (3%)	2 (5%)
Virological breakthrough (n/%)	3 (9%)	4 (9%)
Treatment failure after treatment		
Relapse (n/%)	3 (9%)	1 (2%)

Coilly AASLD 2013

Adverse events

	BOCEPREVIR (n=35)	TELAPREVIR (n=44)	p
Rehospitalization rate (n/%)	9 (26%)	25 (59%)	ns
Rehospitalization for AKI (n/%)	1 (3%)	6 (14%)	ns
Biopsy proven acute rejection	6 (17%)	4 (9%)	ns
Infections	13 (33%)	11 (21%)	ns
Death	3 (8%)	3 (7%)	ns

Coilly AASLD 2013

Hematological toxicity

	BOCEPREVIR (n=35)	TELAPREVIR (n=44)	p
Anemia (Hb<10g/dL)	95%	96%	ns
Anemia (Hb<8g/dL)	63%	45%	ns
RBV dose reduction + EPO use	94%		ns
Red blood cell transfusion	49%		ns
Neutropenia (NC<1G/L)	73%	45%	0.011
GCSF use	19%		ns
Thrombopenia (Plat<50G/L)	48%	28%	ns
Eltrombopag use	6%		ns

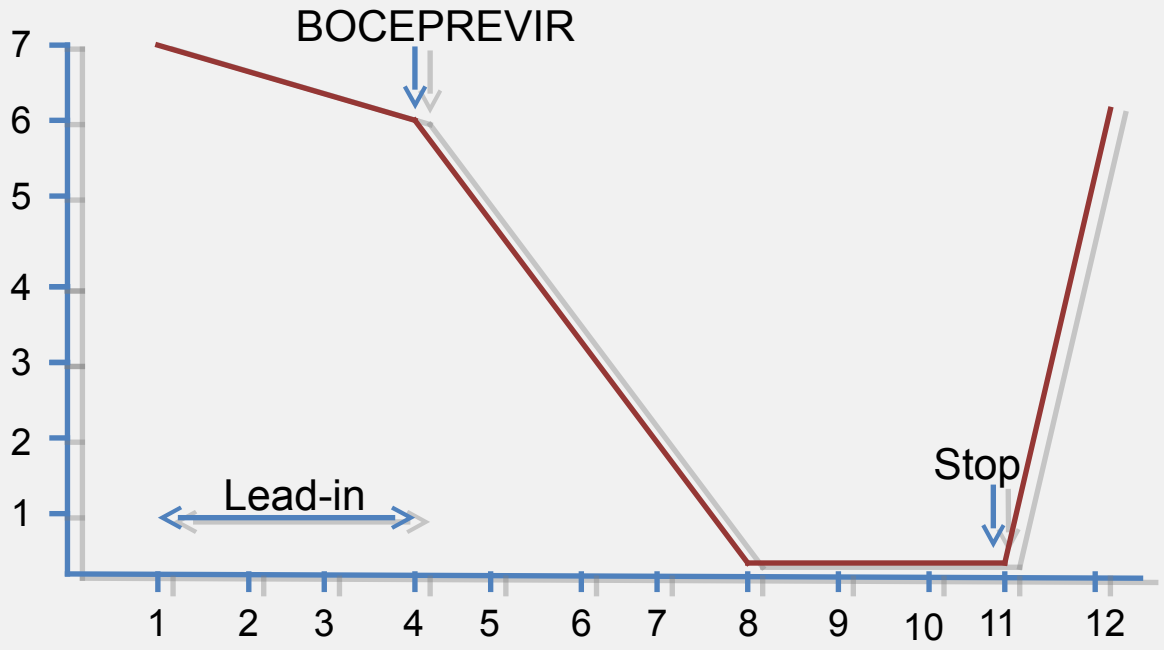
Coilly AASLD 2013

Predictive factors of infection

		Univariate (p)	Multivariate (p/OR/95% CI)	
Before treatment				
Baseline status	BMI	0.167		
	FCH	**0.032**	**0.0473**	**0.22 [0.05-0.98]**
	Bilirubinemia	0.003		
	Hemoglobin	0.152		
	Creatinine clearance	0.158		
Treatment	Peg-IFN a2b	0.067		
	Number of IS drugs	0.090		
	Ciclosporine	0.141		
During treatment				
Anemia <8g/dL		0.039		
Thrombopenia <100 G/L		0.010		

Case

- Stop treatment
- Favorable outcome after 2 weeks with antibiotics
- Relapse after treatment discontinuation…



Case

What do you propose?

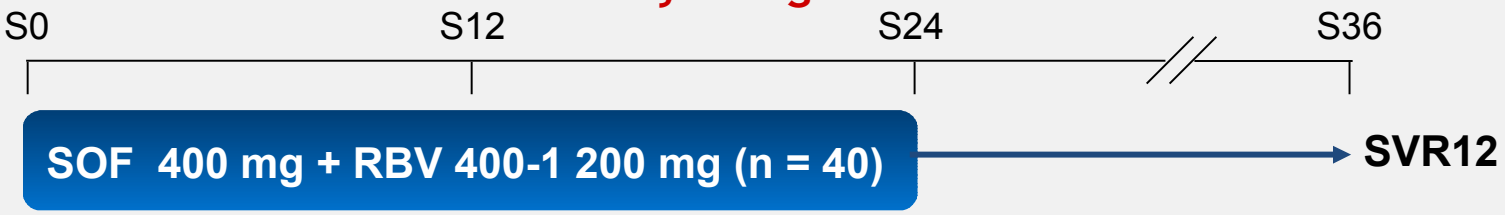
1. Peg-IFN + RBV therapy
2. Triple therapy based on a 1st generation Protease Inhibitors (PI)
3. IFN free regimen

Experience with second generation DAA

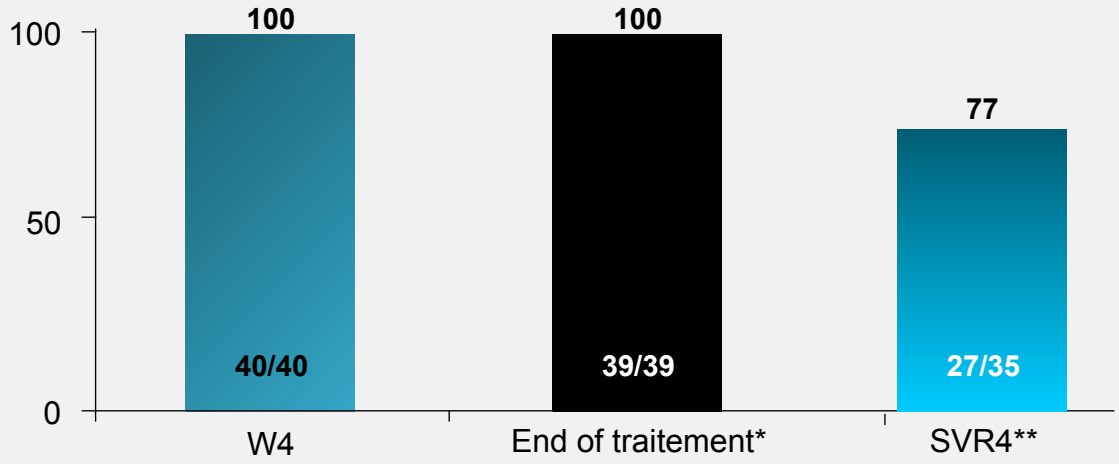
Sofosbuvir + ribavirine for HCV recurrence after LT

- Multicentric prospective study: 40 patients (6-150 month post-LT)
  - G1 (83 %), fibrosis ≥ F3 (63 %), previously treated (88 %)
  - No inclusion if decompensated cirrhosis, steroids > 5 mg/d, Child-Pugh >7, MELD > 17
  - Immunosuppression : tacrolimus (70 %), cyclosporine (25 %)

Study design



Virological reponse



* 1 patient is still under treatment
** 4 patients did not reach the W28 visit

Charlton M, AASLD 2013, Abs. LB2

Sofosbuvir + ribavirine for HCV recurrence after LT

Safety

n (%)	SOF + RBV (n = 40)
Severe adverse events	6 (15)
Adverse events > 15 % of patients	
Fatigue	11 (28)
Cephalalgia	10 (25)
Arthralgia	9 (23)
Diarrhea	9 (23)
Cougg	7 (18)
Nausea	7 (18)
Anemia	6 (15)

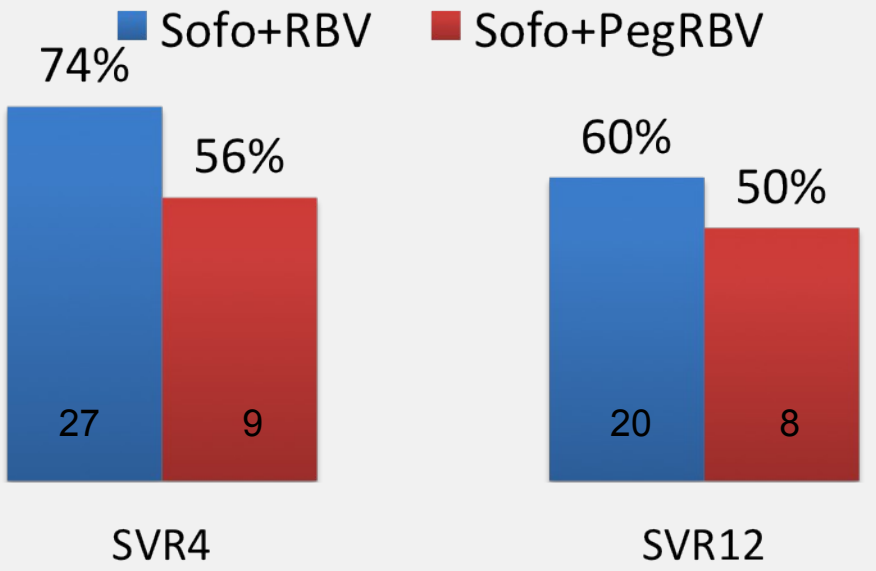
- No death, no graft loss, no rejection

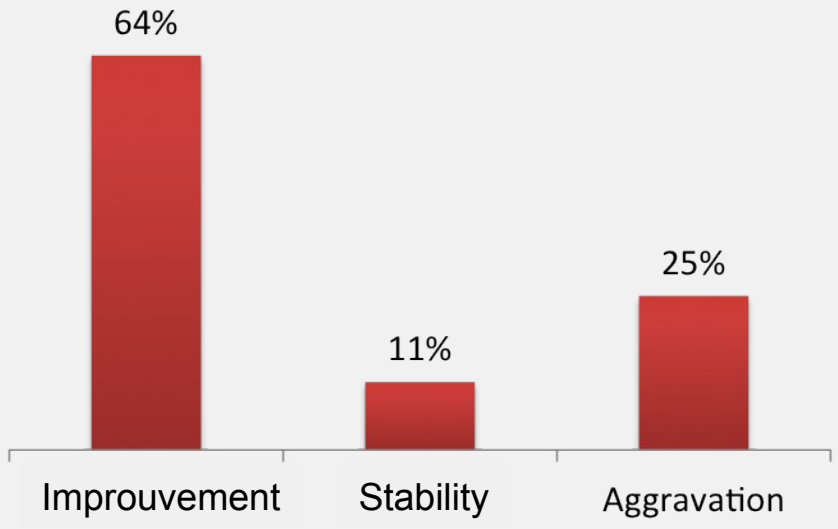
➔ This study demonstrates the efficacy and tolerability of the combination sofusbivir + ribavirin in the treatment of HCV recurrence after LT

Charlton M, AASLD 2013, Abs. LB2

Sofo + RBV post LT (compassionate use)

- 44 patients treated with Sofo+RBV+/-Peg-IFN (n=12),
- Severe recurrence post LT (Mean MELD 16), including 20 pts FCH
- 77% G1

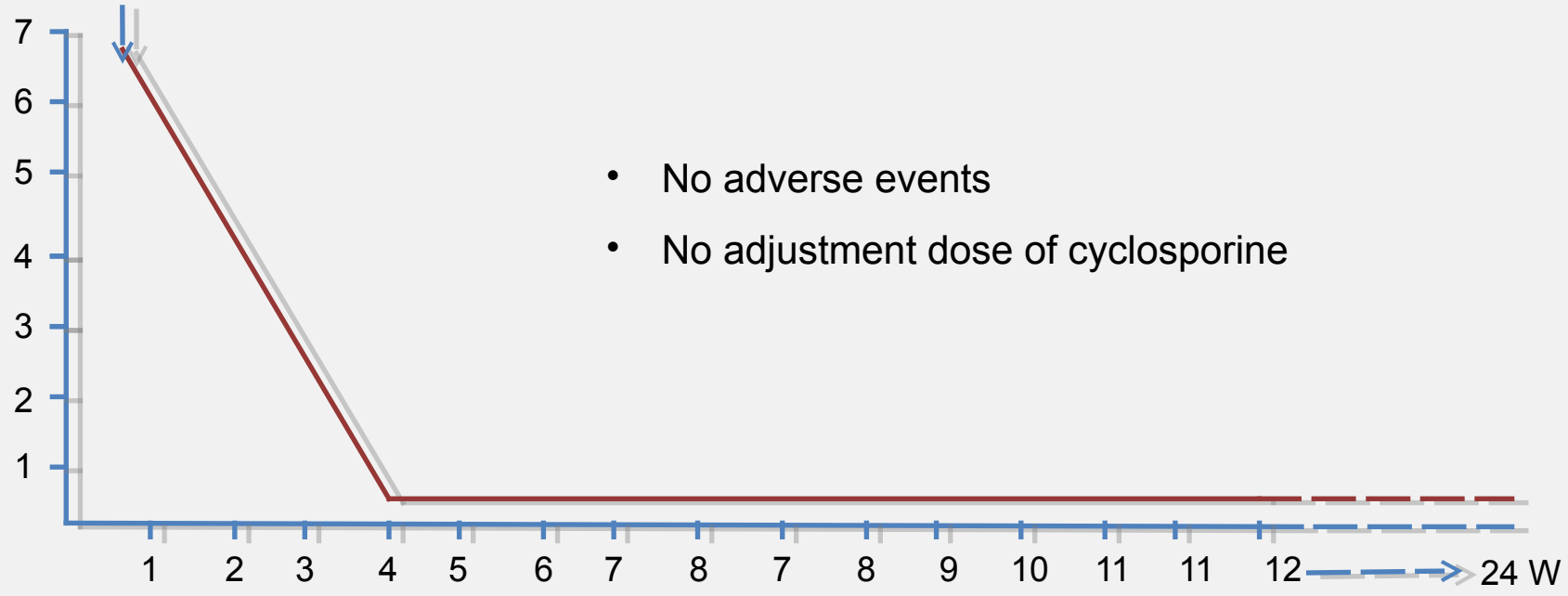




Forns AASLD 2013

Case

SOFOSBUVIR+RIBAVIRIN
(Compassionate temporary use authorization)



- No adverse events
- No adjustment dose of cyclosporine

Conclusion

- Triple therapy including a first generation PI have opened a new era in post-LT treatment of HCV recurrence
- Efficiency looks better than dual therapy
- But: - Poor tolerance (serious adverse events)
  - Drug Interactions (expertise)

- This strategy should be quickly modify in favor of second generation DAA…
  - → Protocols
  - → Prospective cohort including the use of second generation DAA (CUPILT)