ELITA Practical Guidelines on the use of DAAs in Liver transplant candidates and recipients

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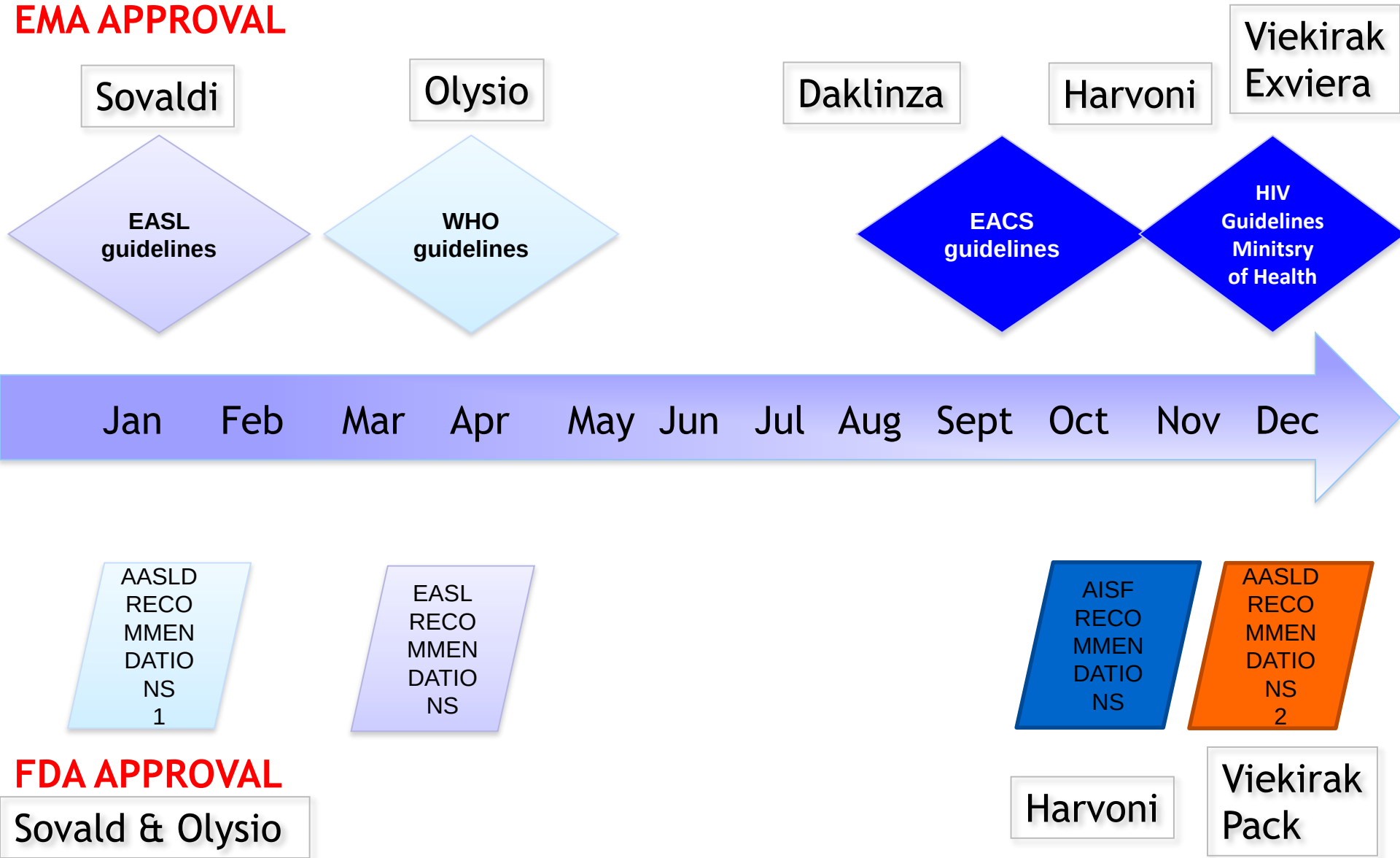
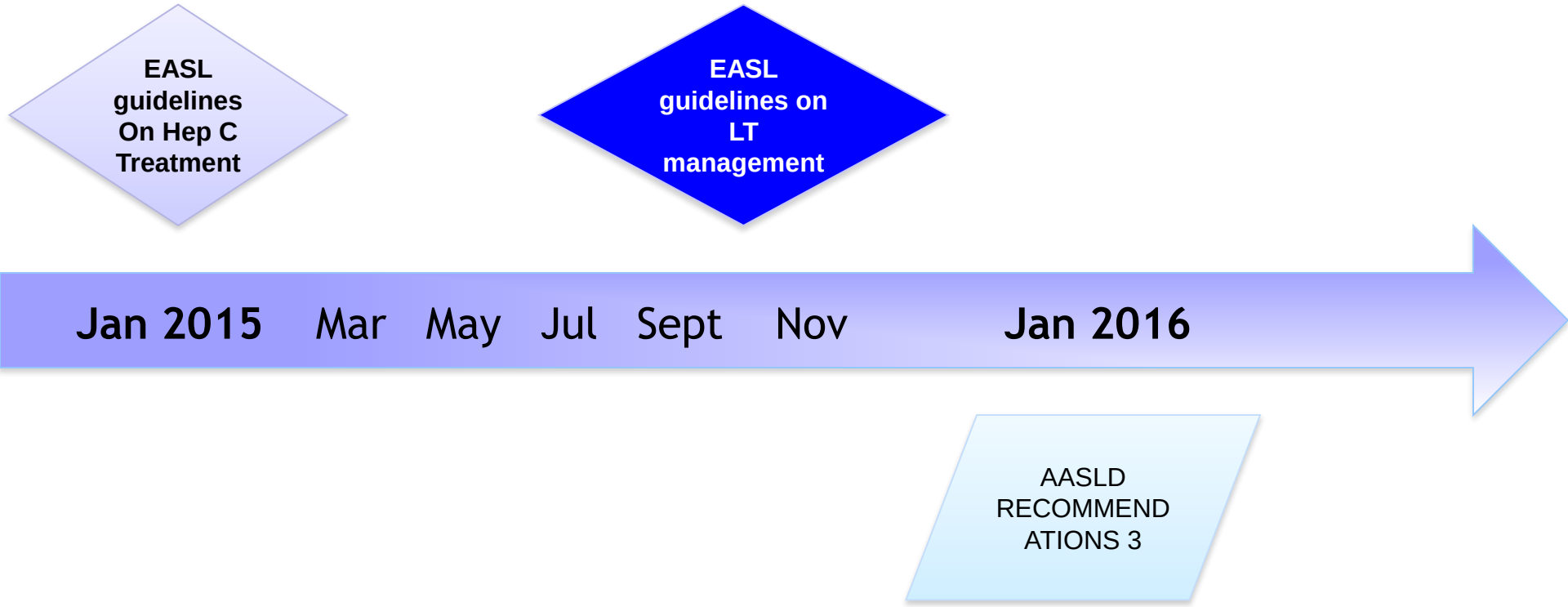
Why the ELITA guidelines?

2014: HCV guidelines, anti HCV drugs approval by International agencies



2015-16: HCV guidelines & anti HCV drugs approval by International agencies

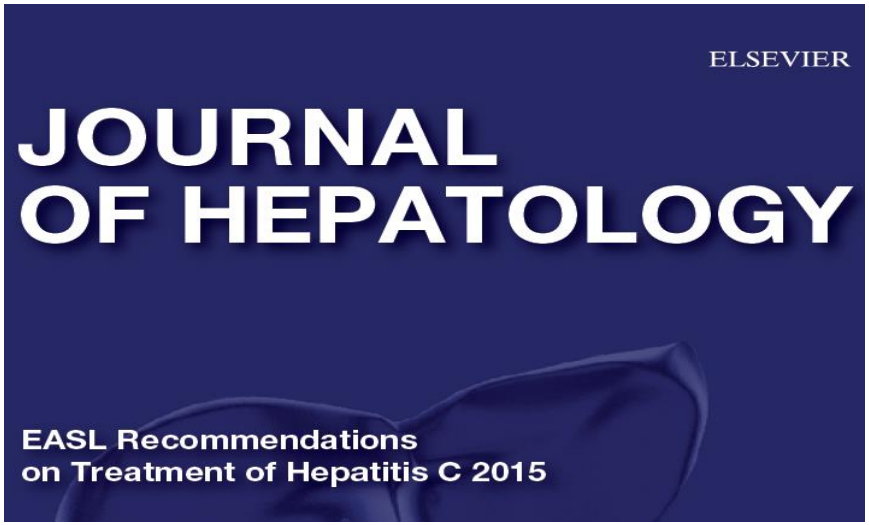
EMA APPROVAL



FDA APPROVAL

Elbasvir & Grazoprevir
Zepatier

- In patients awaiting liver transplantation, antiviral therapy is indicated, because it prevents graft infection **(A1)**
- Treatment should be initiated as soon as possible in order to complete a full treatment course before transplantation and assess the effect of viral clearance on liver function, because significant improvement in liver function may lead to delisting selected cases **(B1)**
- Patients awaiting liver transplantation should be treated with an IFN-free regimen, in principle for 12 or 24 weeks, practically up to transplantation, with ribavirin **(A1)**
- Patients with conserved liver function (Child-Pugh A) in whom the indication for transplantation is HCC can be treated with the combination of sofosbuvir and ribavirin for 16–20 weeks (genotype 2), with the fixed-dose combination of sofosbuvir and ledipasvir with ribavirin for 12 weeks (genotypes 1, 4, 5 or 6), with the combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir with ribavirin for 12 weeks (genotype 1b) or 24 weeks (genotype 1a), with the combination of ritonavir-boosted paritaprevir and ombitasvir with ribavirin for 12 weeks (genotype 4), with the combination of sofosbuvir and simeprevir with ribavirin for 12 weeks (genotypes 1 and 4), or with the combination of sofosbuvir and daclatasvir with ribavirin for 12 weeks (all genotypes) **(B1)**
- Treatment with PegIFN-α, ribavirin and sofosbuvir for 12 weeks is acceptable in patients with compensated (Child-Pugh A) cirrhosis awaiting liver transplantation if IFN-free combinations are not available **(B2)**
- Patients with decompensated cirrhosis (Child-Pugh B or C) awaiting liver transplantation can be treated with the combination of sofosbuvir and ribavirin for 12 weeks (genotype 2), with the fixed-dose combination of sofosbuvir and ledipasvir with ribavirin for 12 weeks (genotypes 1, 4, 5 or 6), or with the combination of sofosbuvir and daclatasvir with ribavirin for 12 weeks (all genotypes); however, data are limited in patients with Child-Pugh C cirrhosis >12 points or with a MELD score >20 **(A1)**
- The optimal timing of treatment (i.e. before transplantation or post-transplantation) to maximize survival is still debatable and requires individual assessment **(B2)**
- Due to the limited amount of safety data reported in patients with decompensated cirrhosis awaiting liver transplantation, frequent clinical and laboratory assessment is necessary **(B2)**



EASL | JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines: Liver transplantation☆

European Association for the Study of the Liver*

Recommendations:

- To reduce the risk of HCV recurrence LT candidates should be treated before transplant (**Grade I**)
- The achievement of negative HCV viral load can improve liver function either before (**Grade II**) or after transplant (**Grade III**)
- New IFN-free antiviral therapies are better tolerated and are a promising option for decompensated cirrhosis (**Grade I**). Sofosbuvir, ledipasvir and daclatasvir can be used in patients with decompensated liver disease (simeprevir in patients with Child-Pugh B) (**Grade II**)
- Patients that could not be treated before LT need to be treated afterwards (**Grade III**)

Recommendations:

- Antiviral therapy is recommended for all patients with hepatitis C recurrence; treatment should be initiated early in those with significant graft damage (F ≥2). SVR is associated with improved outcomes in these patients (**Grade II-1**)
- Treatment with PegIFN and RBV has a low efficacy (SVR ~35%) and is no longer recommended in this setting (**Grade II-2**). The addition of a first generation protein inhibitor (boceprevir, telaprevir) for genotype 1-infected patients increases efficacy but also side effects and is no longer recommended in LT recipients (**Grade II-2**)
- Sofosbuvir/ledipasvir plus RBV and sofosbuvir plus simeprevir (with or without RBV) are safe and achieve high SVR rates in genotype 1- and 4-infected LT recipients, including cirrhotic patients. Sofosbuvir alone or in combination with ledipasvir has also shown to be safe and efficacious in severe forms of recurrence (i.e., fibrosing cholestatic hepatitis) (**Grade II-1**). In naïve patients with mild recurrence, the combination of ABT450/r, ombitasvir, dasabuvir and RBV has shown high efficacy, but cyclosporine and Tac adjustments are necessary due to drug-drug interactions (**Grade II-1**)
- Other IFN-free regimens are being evaluated in clinical trials (**Grade III**)
- More data on drug pharmacokinetics and drug-drug interaction studies are required in LT recipients (**Grade III**)

P Burra et al. J Hepatol 2015

Many issues not covered by “conventional guidelines”

- Treat before or after LT?
- Is delisting possible under DAAs?
- Is bridge therapy feasible?
- Should we expect a more extensive use of anti HCV +ve donors?
- Will ReLT become a more practical option?

ELITA Recommendations on DAAs use in the transplant setting

- A monothematic ELITA Conference was held in Milan on 6 March 2015 where experts from various European countries discussed the many unsolved issues regarding the use of DAAs before and after liver transplantation.

- These recommendations take into account the conclusions of that discussion and the data from the Literature up to Decembre 2015.

Milan Monothematic Conference on DAAs use in liver transplantation.

ELITA GUIDELINES 2015/16

ELITA coordinators. Luca S Belli and Christophe Duvoux

External Panelists.
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External reviewers.
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These guidelines have been presented at the "ELITA Specialty Update Symposium" **held in Brussels on September 13, 2015 and will be submitted for publication.**

ELITA Recommendations: methods

- Coordinated by 2 members of the ELITA Governing Board.
- Based as far as possible on evidence from existing publications or presentations, and, if evidence was unavailable the expert provided personal opinion.
- Where possible the level of evidence and strength of recommendations are provided according to the GRADE SYSTEM.

Table 1. Evidence grading used (adapted from the GRADE system).

Evidence quality	Notes	Grading
High	Further research is very unlikely to change our confidence in the estimate of effect	A
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate	B
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any change of estimate is uncertain	C
Recommendation	**Notes**	**Grading**
Strong	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost	1
Weak	Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption	2

Questions: pre-LT phase

1. Which DAAs should be used in cirrhotic patients listed for LT? **a.** patients with DC **b**. patients with HCC.
2. Which treatment schedules are to be used in listed patients and what is the expected SVR.?
3. What is the impact of DAAs on inactivation/delisting?
4. What is the impact of pre LT DAAs treatment on HCV recurrence post LT?
5. Who should be treated before LT: patients with DC.
6. Who should be treated before LT: patients with HCC
7. Is “bridging therapy” a valuable option?

Questions: pre-LT phase

1. Which DAAs should be used in cirrhotic patients listed for LT?
   - patients with HCC and compensated cirrhosis
   - patients with Decompensated Cirrhosis

2. Which treatment schedules are to be used in listed patients and what is the expected SVR.?

Recommendations

R1. Sofosbuvir, ledipasvir,and daclatasvir can be used in patients with cirrhosis with no need of dose adjustment, whatever the liver impairment (A1).

R2. The 3D combo (Paritaprevir/r, ombitasvir, dasabuvir), the 2D combo (Paritaprevir/r, ombitasvir) should not be used in patients with moderate to severe (Child-Pugh B and C) hepatic impairment. Simeprevir is not recommended in patients with moderate hepatic impairment (Child-Pugh B) and should be avoided in Child-Pugh C (A1). The 3D, 2D combo and Simeprevir can be safely used in Child-Pugh A (B1).

R3. Sofosbuvir requires dose adjustment in case of eGFR< 30 mL/min (every other day) and in patients on hemodialysis (B2). In case severe kidney impairment, treatment with Sofosbuvir is preferably administered after LT

R4. Careful evaluation of Drug Drug interactions with antiretrovirals and other concomitant treatment s is mandatory before starting any anti HCV treatment

R5. Virological response after DAA therapy is very high, in the order of 90%, in patients with compensated cirrhosis (Child-Pugh A) and high, in the order of 80%, in those with decompensated cirrhosis (Child-Pugh B-C) and is not influenced by HIV coinfection: therefore DAA therapy can be considered in patients who are listed for LT (A1).

R6. Since patients with advanced liver disease (Child-Pugh B and C) are at risk of dying before LT and their chances to receive a graft increase with their priority on the waiting list, the duration of DAA treatment should be as short as possible. Therefore, DAA combinations achieving a SVR in 12 weeks should be preferred. (A2)

R7. For listed patients with Child-Pugh A cirrhosis, HCV-RNA clearance of at least 1 month duration seems to be a reliable virological end point to proceed with LT with a low risk (<5%) of viral recurrence after LT. Whether the same virological end point also holds true for patients with decompensated cirrhosis needs to be confirmed. (expert opinion)

R8. First line treatment options for listed patients .....

R9. The treatment options are the same for HIV coinfected patients

Questions: pre-LT phase

1. Which DAAs should be used in cirrhotic patients listed for LT?
   - patients with HCC and compensated cirrhosis
   - patients with Decompensated Cirrhosis

2. Which treatment schedules are to be used in listed patients and what is the expected SVR.?

New comers

VELPATASVIR

GRAZOPREVIR and ELBASVIR

Questions: pre-LT phase

3. What is the impact of DAAs on inactivation/delisting?

ELITA Multicentre study on delisting

Recommendations

R10. In Child B patients a significant improvement of either Child-Pugh (> 2 points) or MELD score (> 3 points) can be achieved in 20 to 40% of the cases. Although this issue is still largely uncovered, preliminary data indicate that delisting is possible in at least 15% of treated patients. Further studies are also needed to assess possible predictors for delisting and which patients might benefit best from DAA treatment. (B1)

R11. In Child Pugh C patients with a MELD score < 25, a similar significant improvement of either Child-Pugh score or MELD can be achieved. However, this improvement may not be sufficient to lead to delisting and it may hamper the access to LT. Further studies are required

Questions: pre-LT phase

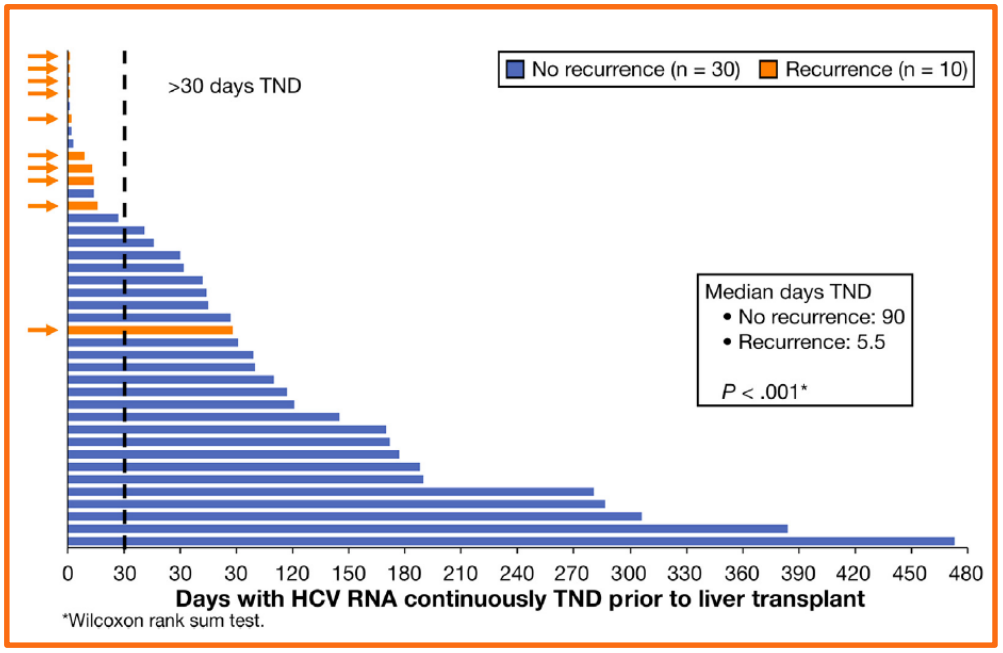
4. What is the impact of pre LT DAAs treatment on HCV recurrence post LT?

1- What is the impact of pre LT DAA on prevention of HCV recurrence post-LT ?

61 HCC-HCV LT candidates receiving SOF+RBV before LT
43 pts (70%) with HCV RNA negative at LT

Table 2. Post-Transplant Virologic Response by Visit for Patients With HCV-RNA Level Less Than the LLOQ at the Last Measurement Before Liver Transplantation

	Sofosbuvir-ribavirin for ≥12 weeks (N = 32)	Sofosbuvir-ribavirin for any duration (N = 43)
Post-transplant week 1		
<LLOQ, n/N (%)	28 (88%)	37 (86%)
90% CI	74%–96%	74%–94%
Post-transplant week 2		
<LLOQ, n/N (%)	26 (81%)	35 (81%)
90% CI	66%–92%	69%–90%
Post-transplant week 4		
<LLOQ, n/N (%)	24 (75%)	31 (72%)
90% CI	59%–87%	59%–83%
Post-transplant week 8		
<LLOQ, n/N (%)	24 (75%)	31 (72%)
90% CI	59%–87%	59%–83%
Post-transplant week 12		
<LLOQ, n/N (%)	24 (75%)	30 (70%)
90% CI	59%–87%	56%–81%



Curry et al. Gastroenterology 2015

Recommendations

R13. Based on current knowledge, prevention of post LT recurrence based on pre LT DAA treatment requires a minimal period of virological suppression of 30 days. This means that whenever possible patients on treatment should be placed "on hold" until this goal is achieved. A period "on hold" of 3 months is generally adequate for most treated patients (B2)

R14. Since recommendation 10 is based on a single study in Child-Pugh A patients receiving a combination of SOF/RBV, further studies are required to confirm the efficacy of other DAA combinations in patients with more advanced diseases and to confirm the validity of the 30-day clearance rule. (B1)

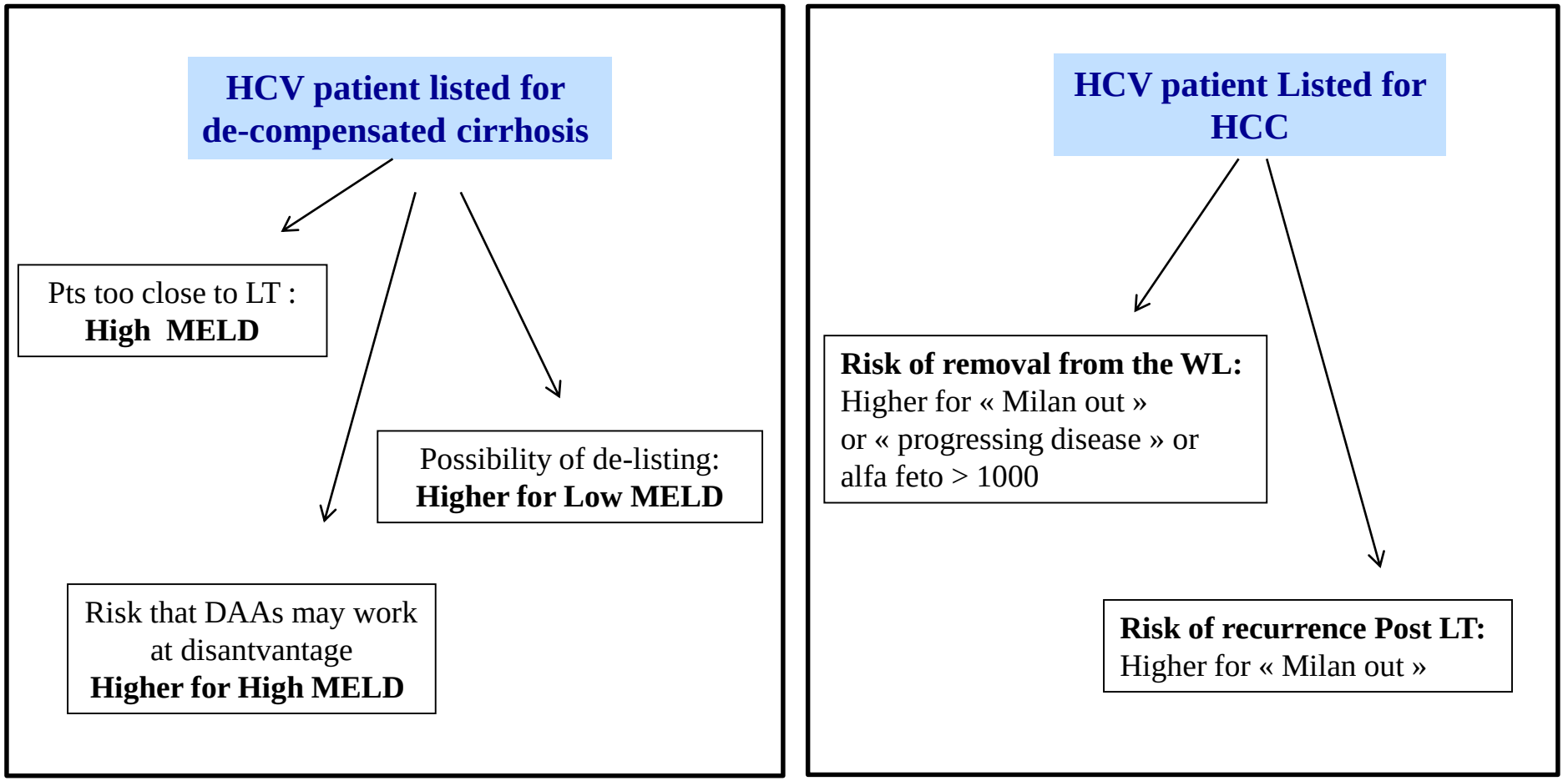
Questions: pre-LT phase

5& 6. Who should be treated before LT

a. patients with DC.

b. patients with HCC

Factors to be taken into account in the decision making process before DAA treatment



→ **Avoid futile DAA treatment**

Recommendations

R15. Based on current studies and practice, pre LT DAA treatment is not recommended in patients with high MELD scores (> 25) because of their poor prognosis due to a significant risk of death either pre and post-LT, unknown probability of improvement, and rapid access to LT. In these patients the option of post LT treatment with DAAs is preferable (expert opinion).

R16. In Child-Pugh B patients the probability clinical improvement and regression of signs of decompensation makes DAA treatment before LT a reasonable option as some of these patients can be delisted.

R17. In Child-Pugh C patients with a MELD <25, an improvement of either Child-Pugh score or MELD by 2-3 points can be achieved in 20 to 40% of the cases. However this improvement may not be sufficient to achieve delisting and again may limit access to LT. The decision whether to treat these patients should therefore be cautious, making sure that it will not be detrimental to the patient. (B2)

R18 Further studies are required to determine possible predictors of delisting and cut-offs of MELD score beyond which DAA would be detrimental for the patients. (expert opinion

Q5b. Patients listed for HCC: who should be treated or not treated before LT?

16- a decision-making algorithm has been suggested where pre LT treatment is restricted to those patients listed for HCC with the following features:

- a low risk of post-transplant HCC recurrence, whatever assessed.
- no signs of HCC progression while on bridging therapy.
- provided that a waiting time > 3 months can be expected

(**expert opinion**)

Questions: pre-LT phase

7. Is “bridging therapy” a valuable option?

Q6: Is DAA bridging therapy a valuable option?

R16- Because of the above-mentioned restrictions, bridging therapy cannot recommended on a routine basis (**Expert opinion**)

R17-In case of unexpected rapid deterioration of liver function due to incidental events, in still viremic patient or in patients who did not achieve viral clearance for at least 30 days, across therapy can be considered but the decision of going on with early post LT DAA treatment and timing of treatment should take into account early liver graft function, post operative renal function and drug to drug interactions. **(Expert opinion)**

Thanks!!!