New regimens for post transplant HCV disease recurrence: ELITA recommendations.

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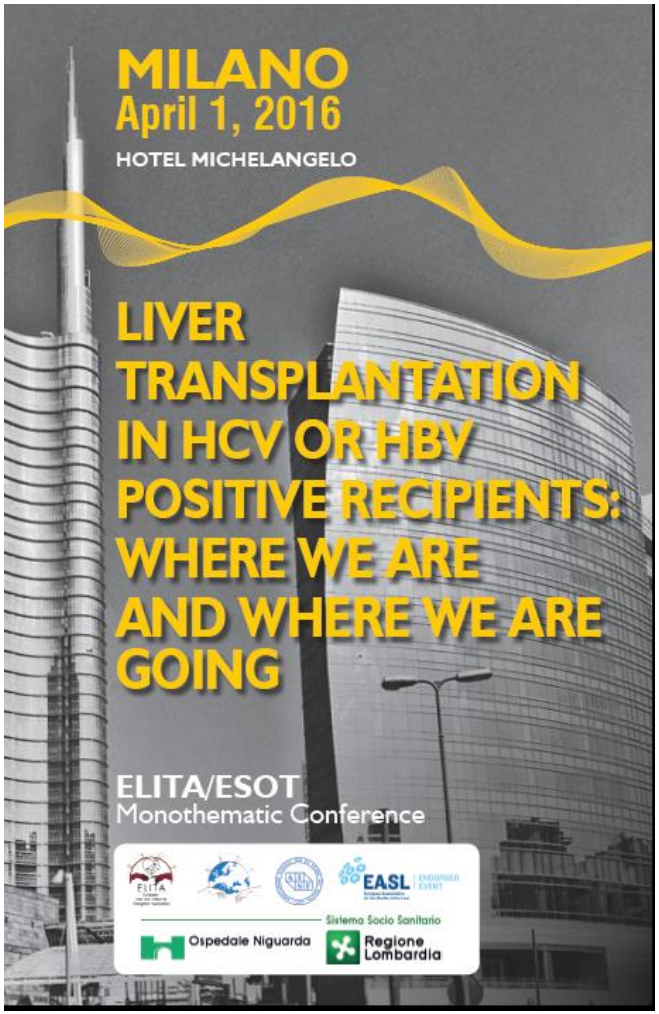


Main issues: Post LT phase

Question 8.

Which are the preferred DAAs after LT, taking into account the specific post-transplant environment (liver function, renal function and drug-to-drug interactions)?

Question 9

What is the expected sustained virological response rate in patients treated with DAAs for post-LT HCV recurrence?

Question 10

Which is the best timing for treatment post-OLT ?

pre-emptive vs early before significant fibrosis vs clinically oriented.

Question 11

Can we expect a beneficial impact of HCV therapy on extra hepatic HCV-associated co-morbidities, irrespective of liver injury?

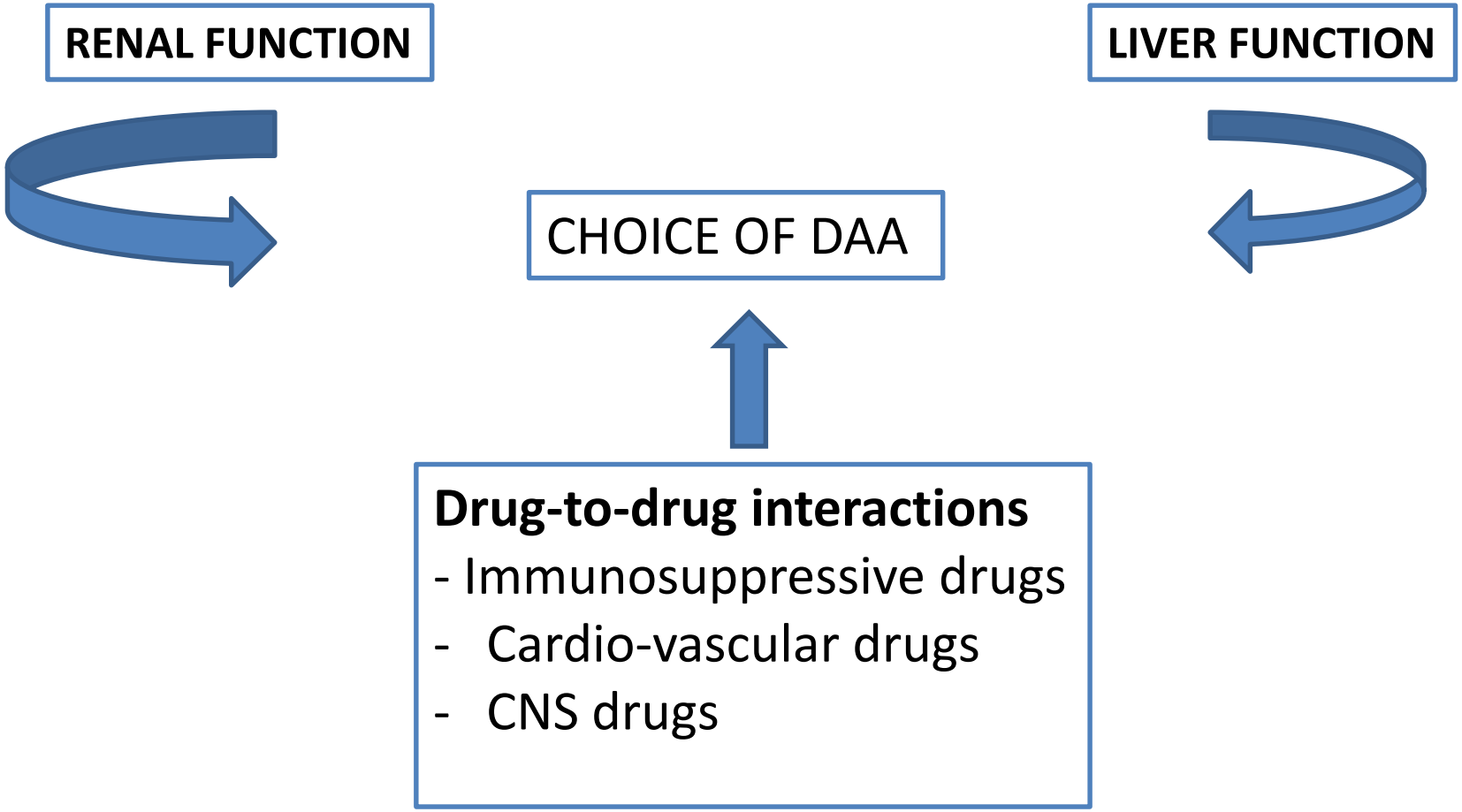
Question 12

Is re-transplantation for HCV-infected recipients a reliable option under DAA therapy?

Question 13

Can HCV positive donors be used more extensively?

Question 8:
Which are the DAA to be preferred post LT taking into account the specific post transplantation environment?



Questions 8: Facts: DDI

	OBV/PTV/r	OBV/PTV/r + DSV	SOF	LED/SOF	DAC	SIM
Ciclosporin	■	■	◆	■	◆	●
Mycophenolate	■	■	◆	◆	◆	◆
Sirolimus	■	■	◆	■	◆	■
Tacrolimus	■	■	◆	■	◆	■

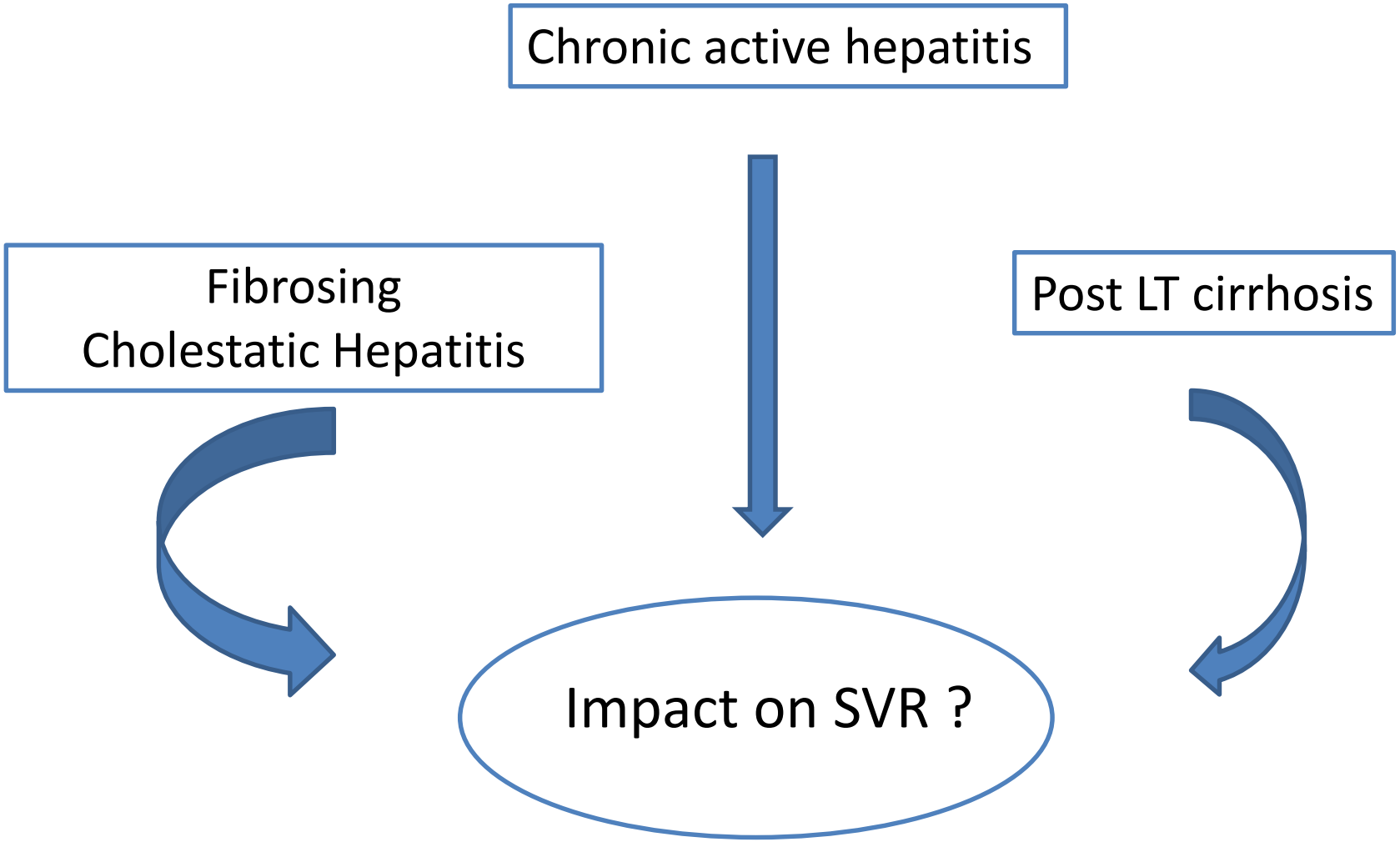
	OBV/PTV/r	OBV/PTV/r + DSV	SOF	LED/SOF	DAC	SIM
Amphotericin B	◆	◆	◆	◆	◆	◆
Caspofungin	◆	◆	■	■	■	■
Fluconazole	◆	◆	◆	◆	◆	●
Itraconazole	●	●■	◆	◆	■	●
Ketoconazole	●	●■	◆	◆	■	●
Posaconazole	●	●■	◆	◆	■	●
Voriconazole	●	●■				
Azithromycin	◆	◆	◆	◆	◆	◆
Clarithromycin	●	●■	◆	◆	■	●

Cortesy of Dr Khoo

Question 8 : Recommendations

- **R22**. SOF (LEDI) and DAC can be combined safely with any immunosuppressants since no clinically significant DDI is expected. Simeprevir should not be co-administered with CsA. **A2**
- **R23** Attention should be paid to any other drugs which are co-administered with DAAs after LT**,** *in particular anti-arythmic and anti-fungal agents.* **A2**
- **R24** Careful evaluation of renal function should be performed before DAA initiation and the choice of DAA should take into account the estimated GFR after transplant. SOF requires dose adjustment if estimated GFR is below 30mL/min. **B2**
- **R25** Caution and close monitoring of immunosuppressant blood levels is recommended at the end of DAA therapy because of HCV clearance may accelerate the metabolism of immunosuppressive drugs.(**Expert opinion**)

Question 9: What is the expected virological efficacy of DAA post LT (SVR)?



Question 9: What is the expected sustained virological response rate in patients treated with DAAs for post-LT HCV recurrence?

→ **Facts**

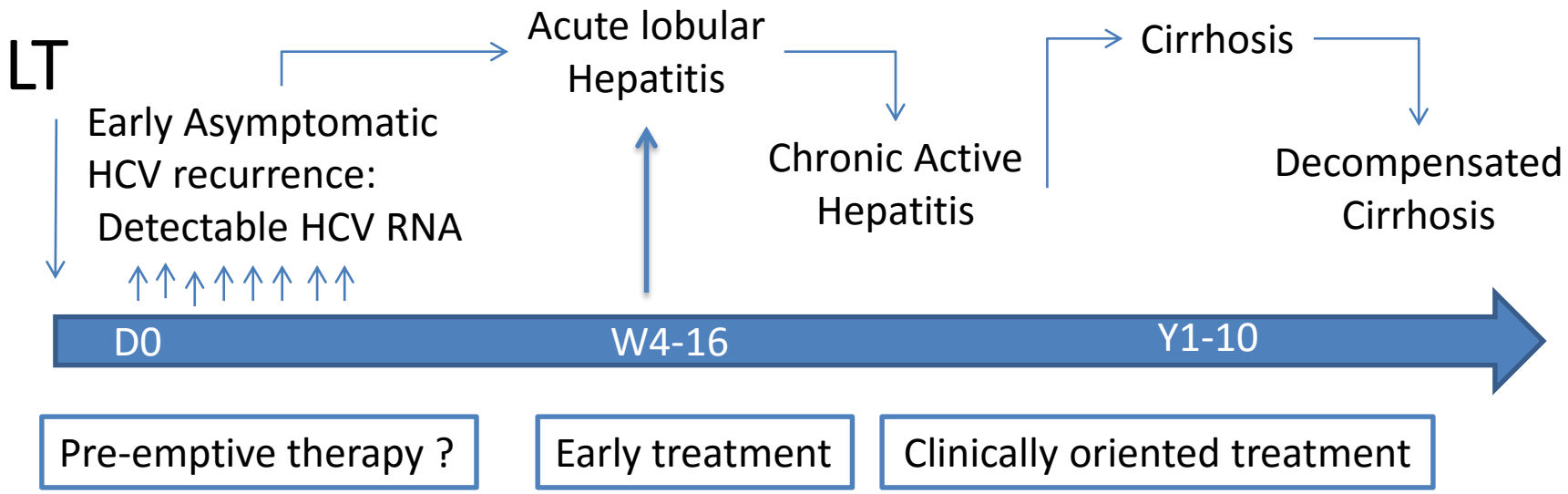
- Highly efficacious regimens are available post-transplant with good safety profile achieving
  - 90 to > 95% SVR12 in non cirrhotics and Child Pugh A pts (SOF+ LEDI/SOF + SIME, 3D), similar to those observed in non transplant pts
  - > 80% in Child Pugh B and around 60% SVR in Child Pugh C
  - With no significant difference between 12 and 24w duration of treatment
- Treatment of patients with early forms of recurrence, including FCH, achieves better virological outcomes than treatment of patients with advanced liver diseases (cirrhosis CP-B and CP-C)

Question 9: Recommendations 26 & 27

- **R27**
  - Given the similar antiviral efficacy of DAA therapy in non-transplanted and LT patients, HCV-infected LT recipients can be treated in the same way as non-transplant patients in terms of HCV genotype and duration of treatment. **A1**

    However, DAA regimens should be adjusted for environmental factors in LT patients, as described in Recommendations 22 to 25

Question 10: What is the best timing for treatment post-OLT ?



Liver function ?
Renal function ?
Viral load

Question 10: Recommendations 28 to 30

- **R28.** At present, pre-emptive DAA therapy cannot be recommended. Prospective studies should be encouraged to assess the benefit of DAA regimens in the very early post-operative phase **(Expert Opinion)**

- **R29** DAA treatment of HCV recurrence should be considered in any LT recipient with evidence of significant early liver injury (i.e. minimal fibrosis stage F1 or necro-inflammatory activity) **A1**

- **R30** Earlier treatment irrespective of the liver fibrosis stage should be considered on a case-by-case basis, taking into account extra-hepatic manifestations of HCV (see Question 11) and cost effectiveness, which may vary from one country to another **(Expert Opinion).**

Question 11: Can we expect a beneficial impact of HCV therapy on extra hepatic manifestations of HCV, irrespective of liver injury?

Question 11: recommendations 31 & 32

R31- A beneficial effect of DAA on extra-hepatic manifestations of HCV post-LT is an attractive hypothesis that may contribute to improved long-term outcomes. The impact of DAA treatment on renal function and insulin resistance post-LT should be considered as secondary endpoints in forthcoming prospective clinical trials or observational studies **(Expert Opinion).**

R32. DAA treatment may be considered on an individual basis in the event of post-LT renal dysfunction or insulin resistance, irrespective of liver injury **(Expert Opinion).**

Question 12: Should retransplantation be considered in patients with severe HCV recurrence ?

Question 12: **Is re-transplantation for HCV-infected recipients a reliable option under DAA therapy?**

Factors affecting survival and decision

-Time to reLT (<1Y or > 1Y)
- Bilirubin > 5 mg/dL
- Renal dysfunction
- MELD > 28
-Burden of HCV recipients

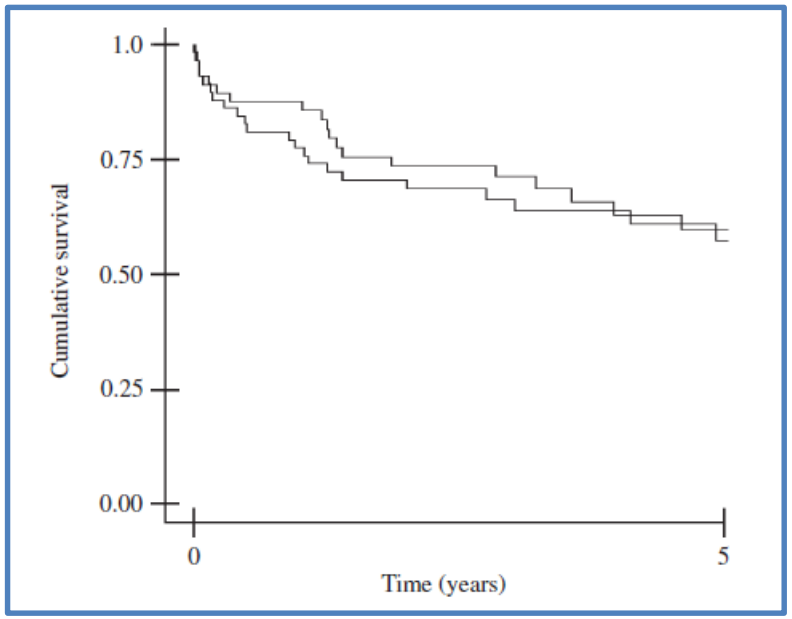
- How DAA therapies may impact the burden and outcome of reLT is unknown so far . This issue has not been addressed in clinical trials.
- Treatment of severe recurrence after primary LT has been reported to improve liver function
- DAA therapies are likely to improve outcome because viral clearance can be achieved either before or after re-transplantation

Question 12 : recommendations 34 & 35

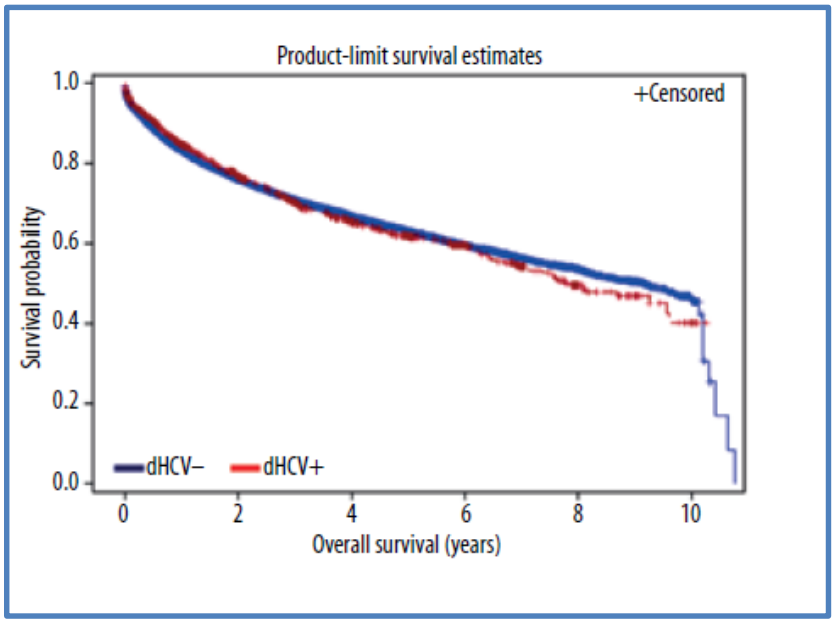
34. Outcome of re-transplantation due to HCV-related primary graft loss should be re-assessed in the DAA era by prospective, observational studies which specifically target this population **(Expert Opinion).**

35. Re-transplantation should be considered on a case-by-case basis, taking into account the intrinsic risks of re-transplantation and organ availability **(B1).**

Question 13 : Can HCV positive organs be used liberally in the DAA era?



Saab et al. AJT 2003



Montenovo et al; Ann Transplant 2015

Prévalence of HCV among donors : 1.4 to 5.5 %

Question 13 : Facts

- Prevalence of HCV among organ donors : 1.4 to 5.5%
- Engraftment of HCV positive liver grafts in HCV +ve recipients has been encouraged by most health authorities on the ground that 5-liver graft survival is similar to that observed with organs from HCV-negative donors. Yet HCV-positive organs have remained under-used
- The high pangenotypic efficacy of DAA regimens may render HCV-positive liver grafts safer and may extend use of such grafts even in HCV-negative recipients (in case of urgent LT for instance), enabling a substantial expansion of the donor pool.
- Recently, the chair of the Ethics Committee of UNOS and the co-chair of the American Society of Transplant Surgeons have both argued for the use of HCV-positive kidneys in HCV- negative recipients

Question 13 : recommendations

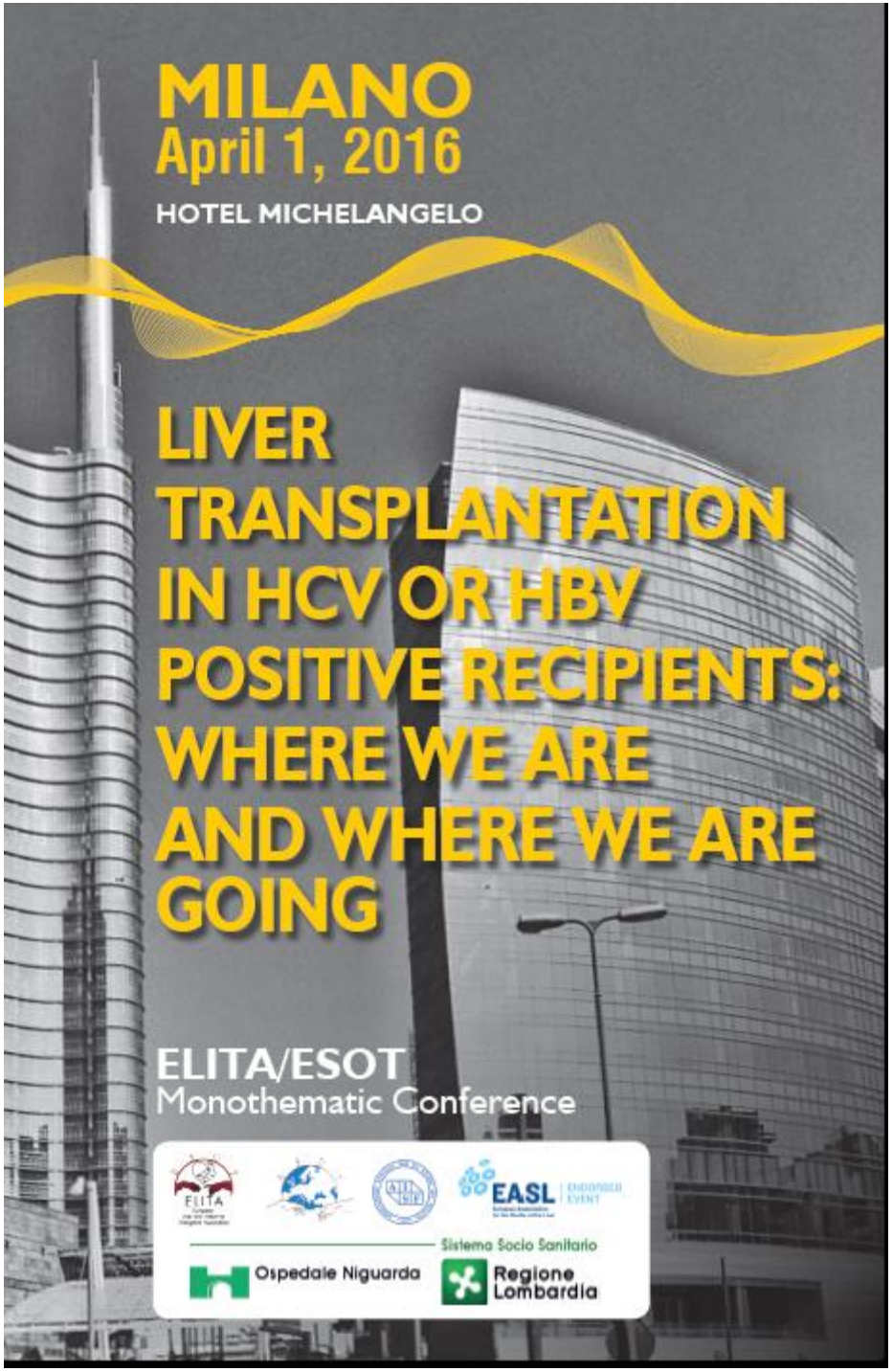
- **R37** Given the high efficacy of DAA, clinical studies under the control of ethical authorities should be designed to prospectively evaluate virological outcomes, and graft and patient survival, in HCV-positive and HCV-negative recipients of HCV-positive liver grafts. **(B1)**

Conclusions

- DAAs are radically changing the management of HCV in the transplantation setting and open a number of amazing doors:
  - Pre LT:
    - Significant rate of SVR to prevent HCV recurrence in appropriately selected patients
    - Delisting can be considered as an option in DDA era
  - Post LT
    - Virtually constant elimination of the virus with an expected impact on long term survival
    - Potential impact on extra hepatic HCV-related co-morbidities
    - Reasonable basis for considering reLT for HCV graft loss
  - Expansion of the donor pool through a larger use of HCV + ve liver grafts

Conclusions 2

- However, some critical issues deserve further clarification to optimize the management of DAA in the LT setting:
  - Best DAA combination in case of renal dysfonction
  - Safety of DAA in patients with severely impaired liver function
  - Reliable predictors of delisting pre LT
  - MELD cut-off beyond which pre LT treatment does not sound reasonable
  - Minimal duration of treatment to prevent HCV recurrence
  - Long-term impact on renal function and insulin resistance
  - Impact on retransplantation outcome
  - Role in the treatment of HCV infected organs
    - Both in HCV +ve and negative recipients


MILANO
April 1, 2016
HOTEL MICHELANGELO
LIVER TRANSPLANTATION IN HCV OR HBV POSITIVE RECIPIENTS: WHERE WE ARE AND WHERE WE ARE GOING
ELITA/ESOT
Monothematic Conference
ELITA
EASL
ENDORSED EVENT
Sistema Socio Sanitario
Ospedale Niguarda
Regione Lombardia

Question 9: Recommendation 26

Treatment of HCV-infected LT recipients can follow the same principles than in non transplant patients regarding genotype

G1 and G4:

- SOF+LDV+/-RBV 12 weeks (clinical trials)
- SOF+SIM (±RBV) 12 weeks (real life)
- 3D+RBV 24 weeks (clinical trials)
- SMV+DAC+RBV 24 weeks (real life)

G2:

- SOF+RBV 12 weeks (real life)

G3:

- SOF+RBV 24 weeks (real life)
- SOF+DAC 24 weeks (real life)

Cortesy of X Forns

Question 11: Can we expect a beneficial impact of HCV therapy on extra hepatic manifestations of HCV, irrespective of liver injury?

- A beneficial impact of DAA on extra-hepatic manifestations of HCV post-LT is an attractive hypothesis that may contribute to long term improvement of LT results.
- The impact of DAA on renal function and glucose metabolism has not been addressed in post-LT phase 3 prospective clinical trials, nor retrospective investigators-driven studies.