Liver transplantation issues in 2018

Minimisation of immunosuppression in the long term: what is it for?

Chairs: Didier SAMUEL (France) Pierre-Alain CLAVIEN (Switzerland)
Speakers: Dominique THABUT (France) Sébastien DHARANCY (France)
Considerable improvements have been made in acute rejection and short-term patient/graft survival.

Acute rejection:
- ~20% in the 1980s
- ~60% in the 1990s
- 90% in the 2010s

Patient survival:
- 5–15% in the 1980s
- 60% in the 1990s
- 90% in the 2010s

药物使用情况（%）:
- Azathioprine
- Prednisone
- CsA
- Tacrolimus
- MMF
- Basiliximab
- Sirolimus
- Everolimus

图中显示了从1975年到2015年，移植后一年患者生存率和急性排斥反应的变化。
Progressive enrichment in drugs leading to a stepwise improvement in survival, but…
Weak improvements have been made in long-term patient survival

What are the exact statements regarding long-term complications after Liver Transplantation?

A / Cardiovascular diseases are the leading cause of non-hepatic mortality after LT

B / De novo cancers are the leading cause of non-hepatic mortality after LT

C / The RR to develop de novo cancer is 2 to 15 fold higher in transplant patients than in the general population

D / Life expectancy after LT is similar than general population
Life expectancy after LT
Stable « survival deficit » as compared with general population

Aberg F et al. Hepatology 2014
The evolving mortality in liver transplantation

Causes of death among LTx recipients > 1 year

- Hepatic: 28%
- Malignancy: 22%
- Cardiovascular: 11%
- Infections: 9%
- Renal Failure: 6%

Renal-related mortality increased dramatically over time:
- 10.2% of deaths after 5 years (greatest increase among the major causes)
- Increased probability after 8 years
- Sharp rise after 10 years

Renal insufficiency/failure was present in 17% of pre-LT, 47% of post-LT by 1 year, and 64% of post-LT patients overall.

Post-transplant renal insufficiency was strongly associated with increased overall mortality beyond 1 year (HR: 4.10, 95%CI: 2.87–5.86; P<0.001)

The evolving mortality in liver transplantation

Causes of mortality after LT in “real life”

The Montpellier LT team center

<table>
<thead>
<tr>
<th>Indications</th>
<th>ALD</th>
<th>HCV</th>
<th>HCC</th>
<th>HBV</th>
<th>Other</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Causes of death</td>
<td>n = 206</td>
<td>n = 74</td>
<td>n = 57</td>
<td>n = 25</td>
<td>n = 79</td>
<td></td>
</tr>
<tr>
<td>Recurrence</td>
<td>13/55 (23.6%)</td>
<td>6/21 (28.6%)</td>
<td>11/19 (57.9%)</td>
<td>1/4 (25%)</td>
<td>10/19 (52.6%)</td>
<td>41/118 (34.7%)</td>
</tr>
<tr>
<td>Non-hepatic cancer</td>
<td>18/55 (32.7%)</td>
<td>5/21 (23.8%)</td>
<td>4/19 (21%)</td>
<td>2/4 (50%)</td>
<td>3/19 (15.8%)</td>
<td>32/118 (27.1%)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>8/55 (14.5%)</td>
<td>2/21 (4.7%)</td>
<td>1/19 (5.3%)</td>
<td>1/4 (25%)</td>
<td>2/19 (10.5%)</td>
<td>14/118 (11.9%)</td>
</tr>
<tr>
<td>Infection</td>
<td>6/55 (10.9%)</td>
<td>4/21 (9.5%)</td>
<td>1/19 (5.3%)</td>
<td>0</td>
<td>1/19 (5.3%)</td>
<td>12/118 (10.2%)</td>
</tr>
<tr>
<td>Rejection</td>
<td>2/55 (3.6%)</td>
<td>2/21 (4.7%)</td>
<td>0</td>
<td>0</td>
<td>1/19 (5.3%)</td>
<td>5/118 (4.2%)</td>
</tr>
<tr>
<td>Others</td>
<td>8/55 (14.5%)</td>
<td>2/21 (4.7%)</td>
<td>2/19 (10.5%)</td>
<td>0</td>
<td>2/19 (10.5%)</td>
<td>14/118 (11.9%)</td>
</tr>
<tr>
<td>Total</td>
<td>55</td>
<td>21</td>
<td>19</td>
<td>4</td>
<td>19</td>
<td>118</td>
</tr>
</tbody>
</table>

Faure S et al. J Hepatol 2012
**De novo cancer after LT**

<table>
<thead>
<tr>
<th>Type of Neoplasia</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>2–4</td>
</tr>
<tr>
<td>Squamous and basal cell skin cancer</td>
<td>20–70</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>10–30</td>
</tr>
<tr>
<td>Head and neck cancer</td>
<td>4–7</td>
</tr>
<tr>
<td>In alcoholic liver disease</td>
<td>25</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>1.7–2.5</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>3–12</td>
</tr>
<tr>
<td>In ulcerative colitis</td>
<td>25–30</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>Not increased</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Not increased</td>
</tr>
<tr>
<td>Kidney cancer</td>
<td>5–30</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>100</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>3.4</td>
</tr>
</tbody>
</table>

Herrero JI et al, Liver Transplant 2005
De novo cancer after LT

Figure 1: Overall cumulative incidence of any de novo cancer (excluding nonmelanoma skin cancer) in the transplanted and general populations.

Collett D, Am J Transplant 2010
**De novo cancer after LT in France**

Table 1. Comparison of the solid cancer incidences post-LT and in the general population. Incidences expressed per 100,000 persons and per annum

<table>
<thead>
<tr>
<th></th>
<th>Solid cancer</th>
<th>Oral cancer</th>
<th>Lung cancer</th>
<th>Digestive cancer</th>
<th>Colorectal cancer</th>
<th>Oesophageal cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hérault registry</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gross incidence</td>
<td>339.8</td>
<td>26.9</td>
<td>49.0</td>
<td>70.1</td>
<td>59.1</td>
<td>6.7</td>
</tr>
<tr>
<td>95% CI lower limit</td>
<td>337.2</td>
<td>26.1</td>
<td>48.0</td>
<td>68.9</td>
<td>58.0</td>
<td>6.3</td>
</tr>
<tr>
<td>95% CI upper limit</td>
<td>342.5</td>
<td>27.6</td>
<td>50.0</td>
<td>71.3</td>
<td>60.2</td>
<td>7.1</td>
</tr>
<tr>
<td>Standardized incidence</td>
<td>203.4</td>
<td>17.8</td>
<td>29.5</td>
<td>39.9</td>
<td>33.3</td>
<td>4.0</td>
</tr>
<tr>
<td>95% CI lower limit</td>
<td>199.4</td>
<td>17.7</td>
<td>29.3</td>
<td>39.6</td>
<td>33.1</td>
<td>4.0</td>
</tr>
<tr>
<td>95% CI upper limit</td>
<td>207.4</td>
<td>17.9</td>
<td>29.7</td>
<td>40.2</td>
<td>33.5</td>
<td>4.0</td>
</tr>
<tr>
<td>LT population</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gross incidence</td>
<td>1310.8</td>
<td>352.9</td>
<td>302.5</td>
<td>327.7</td>
<td>176.5</td>
<td>100.8</td>
</tr>
<tr>
<td>95% CI lower limit</td>
<td>998.8</td>
<td>209.0</td>
<td>171.8</td>
<td>190.3</td>
<td>84.1</td>
<td>37.8</td>
</tr>
<tr>
<td>95% CI upper limit</td>
<td>1720.2</td>
<td>595.9</td>
<td>532.7</td>
<td>564.4</td>
<td>370.1</td>
<td>268.7</td>
</tr>
<tr>
<td>Standardized incidence</td>
<td>760.0</td>
<td>281.4</td>
<td>150.5</td>
<td>145.3</td>
<td>88.8</td>
<td>41.8</td>
</tr>
<tr>
<td>95% CI lower limit</td>
<td>721.7</td>
<td>268.2</td>
<td>148.9</td>
<td>143.7</td>
<td>88.1</td>
<td>41.6</td>
</tr>
<tr>
<td>95% CI upper limit</td>
<td>800.3</td>
<td>295.3</td>
<td>152.1</td>
<td>147.0</td>
<td>89.6</td>
<td>42.1</td>
</tr>
<tr>
<td>Relative risk</td>
<td>3.7</td>
<td>15.8</td>
<td>5.1</td>
<td>4.6</td>
<td>2.7</td>
<td>10.5</td>
</tr>
<tr>
<td>95% CI lower limit</td>
<td>2.8</td>
<td>9.4</td>
<td>2.9</td>
<td>2.6</td>
<td>1.3</td>
<td>3.9</td>
</tr>
<tr>
<td>95% CI upper limit</td>
<td>4.9</td>
<td>26.7</td>
<td>9.0</td>
<td>7.8</td>
<td>5.6</td>
<td>27.9</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.007</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

95% CI = 95% confidence interval

Study including 322 recipients

*Carencq C, Liver Int 2015*
Survival is impaired in case of *de novo* cancer after Liver Transplantation

Overall survival of patients who developed solid cancers or not

Study in 322 recipients

Carencio C, Liver Int 2015
What are the exact statements regarding long-term complication after Liver Transplantation?

A/ Cardiovascular diseases are the leading cause of non-hepatic mortality after LT

B/ De novo cancers are the leading cause of non-hepatic mortality after LT

C/ The RR to develop de novo cancer is 2 to 15 fold higher in transplant patients than in the general population

D/ Life expectancy after LT is similar than general population
Immunosuppression after LT:
good intentions, accelerating life countdown…
What’s CNI minimization?

A / Tac C0 Levels 10-15 ng/mL
B / Tacrolimus withdrawal
C / Target Tac C0 levels at 5 ng/mL
D / Tac C0 levels 5-8 ng/mL
E / Immunosuppression withdrawal
**Immunosuppression withdrawal because liver is a « tolerogenic organ » !**

**TABLE 2. Elective Withdrawal Studies**

<table>
<thead>
<tr>
<th>Center (No. of Patients)</th>
<th>Adult or Pediatric</th>
<th>DDLT or LDLT</th>
<th>Baseline IS</th>
<th>Years from LT to Tapering</th>
<th>Tolerant (%)</th>
<th>Failure (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pittsburgh (n = 95)</td>
<td>Both</td>
<td>DDLT</td>
<td>TAC or CyA + AZA</td>
<td>Mean, 8.4 ± 4.7</td>
<td>18 (18.9%)</td>
<td>40 (42.1%)</td>
</tr>
<tr>
<td>London (n = 18)</td>
<td>Adult</td>
<td>DDLT</td>
<td>CyA, AZA, prednisolone</td>
<td>Median, 7 (5-11)</td>
<td>5 (27.7%)</td>
<td>13 (72.2%)</td>
</tr>
<tr>
<td>Kyoto (n = 115)</td>
<td>Pediatric</td>
<td>LDLT</td>
<td>TAC</td>
<td>&gt;2 years</td>
<td>49 (42.6%)</td>
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<td>Murcia (n= 9)</td>
<td>Adult</td>
<td>DDLT</td>
<td>CyA</td>
<td>Median, 5.1 (2-9)</td>
<td>3 (33.3%)</td>
<td>6 (66.6%)</td>
</tr>
<tr>
<td>Rome (n = 34, only HCV)</td>
<td>Adult</td>
<td>DDLT</td>
<td>CyA</td>
<td>Mean, 5.3 ± 1.7</td>
<td>8 (23.5%)</td>
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<tr>
<td>New Orleans (n = 18)</td>
<td>Adult</td>
<td>DDLT</td>
<td>TAC</td>
<td>&gt;0.5 years</td>
<td>1 (5.6%)</td>
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</tr>
<tr>
<td>Winnipeg (n = 26)†</td>
<td>Adult</td>
<td>DDLT</td>
<td>CyA + AZA or prednisolone</td>
<td>Mean, 4.3 ± 1.1</td>
<td>8 (30.8%)</td>
<td>18 (69.2%)</td>
</tr>
<tr>
<td>Miami (n = 104)‡</td>
<td>Adult</td>
<td>DDLT</td>
<td>TAC or CyA</td>
<td>Median, 4 (3.6-4.6)</td>
<td>23 (22.1%)</td>
<td>81 (61.5%)</td>
</tr>
<tr>
<td>Barcelona (n = 102)</td>
<td>Adult</td>
<td>DDLT</td>
<td>TAC or CyA</td>
<td>Median, 7.9</td>
<td>40 (77.9%)</td>
<td>62 (60.0%)</td>
</tr>
</tbody>
</table>

*Either due to rejection, immune-mediated hepatitis, noncompliance, resumption of immunosuppression, disease recurrence, or other. The remaining patients were deemed “weaning in progress” in all studies.

†Randomized controlled trial of ursodeoxycholic acid given at 15 mg/kg/day versus placebo in withdrawing patients; 3 patients developed autoimmune hepatitis recurrence after withdrawal.

‡45 received donor bone marrow cell infusions; 59 did not.
The liver as a tolerogenic organ
More or less!

Lucky!

Lucky!

Unlucky...

IS withdrawal = russian roulette so far...

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<th>Failure*</th>
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Letvisky J et al Liver Transplant 2011
Current concept of CNI minimization

Reduction in Tacrolimus Trough Levels Achieved in Different Studies

What's CNI minimization?

A / Tac C0 Levels 10-15 ng/mL

B / Tacrolimus withdrawal

C / Target Tac C0 levels at 5 ng/mL

D / Tac C0 levels 5-8 ng/mL

E / Immunosuppression withdrawal
Clinical observation (1)

- 58 years old woman
- Past medical history: diabetes, dyslipidemia, smoking 30 pack/year, COPD, appendectomy
- Weight 55 kg, Size 1m68, BMI 19
- LT on October 30 2007 for decompensated alcoholic cirrhosis with hepatorenal syndrome (Child Pugh C10, MELD 24)
- Native liver without HCC
- Immunosuppressive regimen:
  - Solupred withdrawn in May 2008
  - Tacrolimus 6 mg x2 /d (C0: 10 ng/mL)
  - MMF (Cellcept) 1 g × 2/day
What are the *de novo* cancer risk factors identified in this patient?

A / Age > 50 years
B / History of alcoholic liver disease
C / Gender
D / Smoking
E / Exposure to CNI
F / Weight
Environmental risk factors

Table 3. Risk Factors for Solid Organ Malignancy: Multivariate Analysis

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age by decade</td>
<td>1.33 (1.05–1.66)</td>
<td>.014</td>
</tr>
<tr>
<td>Smoking history</td>
<td>1.72 (1.06–2.79)</td>
<td>.029</td>
</tr>
<tr>
<td>ALD</td>
<td>2.14 (1.22–3.73)</td>
<td>.007</td>
</tr>
<tr>
<td>PSC</td>
<td>2.62 (1.50–4.56)</td>
<td>.001</td>
</tr>
</tbody>
</table>

ALD, alcohol-related liver disease; CI, confidence interval; HR, hazard ratio; PSC, primary sclerosing cholangitis.

Study including 798 recipients

Watt KD, Gastroenterology
2009
### Table 2. Risk factors for developing de novo solid cancer post-LT, univariate and multivariate analyses

<table>
<thead>
<tr>
<th>Variable</th>
<th>No solid cancer (N = 400)</th>
<th>Solid cancer (N = 65)</th>
<th>P value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at LT &gt; 50 years</td>
<td>222/400 (55.5)</td>
<td>40/65 (61.5)</td>
<td>0.36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>296/400 (74)</td>
<td>50/65 (76.9)</td>
<td>0.62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excessive OH before LT</td>
<td>241/371 (65)</td>
<td>53/63 (84.1)</td>
<td>0.003</td>
<td>2.9</td>
<td>(1.4; 5.8)</td>
</tr>
<tr>
<td>Excessive OH after LT</td>
<td>44/383 (11.5)</td>
<td>12/64 (18.8)</td>
<td>0.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>142/391 (36.3)</td>
<td>26/64 (40.6)</td>
<td>0.51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking before LT</td>
<td>200/372 (53.8)</td>
<td>54/64 (84.41)</td>
<td>&lt;0.0001</td>
<td>4.6</td>
<td>(2.3; 9.4)</td>
</tr>
<tr>
<td>Smoking after LT</td>
<td>119/370 (37.2)</td>
<td>36/64 (56.3)</td>
<td>0.0002</td>
<td>2.7</td>
<td>(1.6; 4.6)</td>
</tr>
<tr>
<td>Obesity</td>
<td>60/381 (15.8)</td>
<td>17/62 (27.4)</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patients included in the study (N = 465): multivariate analysis of solid cancer risk factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>P value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking before LT</td>
<td>&lt;0.0001</td>
<td>5.5</td>
<td>(2.5; 12)</td>
</tr>
<tr>
<td>Obesity</td>
<td>0.0184</td>
<td>2.2</td>
<td>(1.1; 4.3)</td>
</tr>
</tbody>
</table>

### Table 3. Univariate and multivariate analysis of risks factors for de novo solid cancers post-LT with tacrolimus

Risks factors for de novo solid cancer after LT with tacrolimus

<table>
<thead>
<tr>
<th>Variable</th>
<th>Tacrolimus 1 year (43 with C &amp; 204 without C)</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>P value</td>
<td>OR</td>
</tr>
<tr>
<td>Age &gt;50</td>
<td></td>
<td>0.37</td>
<td>NS</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>0.7</td>
<td>NS</td>
</tr>
<tr>
<td>Alcohol pre-LT</td>
<td></td>
<td>0.07</td>
<td>NS</td>
</tr>
<tr>
<td>Alcohol post-LT</td>
<td></td>
<td>0.27</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td>0.56</td>
<td>NS</td>
</tr>
<tr>
<td>Tobacco pre-LT</td>
<td></td>
<td>0.0001</td>
<td>5.1</td>
</tr>
<tr>
<td>Tobacco post-LT</td>
<td></td>
<td>0.002</td>
<td>2.8</td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
<td>0.12</td>
<td>NS</td>
</tr>
</tbody>
</table>

**CNI level exposure** | *Mean annual tacrolimus blood trough concentration > 8 ng/ml during the first year after LT and > 7 ng/ml during the 3 years after LT. LT, liver transplantation; NS, non-significant; C, cancer. CNI, calcineurin inhibitors.
Smoking and *de novo* cancer

Herrero JL, Liver Transpl 2011
Experimental arguments in favor the linkage between CNI and cancer

Number of lung metastases in a model of renal cancer metastases in SCID mice

Maluccio et al. Transplantation 2003
CNI promotes tumor growth, metastasis and angiogenesis

Guba et al. Transplantation 2004
Tacrolimus and the Risk of Solid Cancers After Liver Transplant: A Dose Effect Relationship


First published: 3 February 2015

Full publication history
CNI exposure and the risk of solid cancers after LT
A dose effect relationship

Relationship between mean TC during the first year and occurrence of solid cancers

What are the *de novo* cancer risk factors identified in this patient?

A / Age > 50 years

B / History of alcoholic liver disease

C / Gender

D / Smoking

C / Exposure to CNI

D / Weight
Clinical observation (2)

- October 2012 (5 years post LT)
- Gradual development of chronic renal dysfunction
  - eGFR at 40 mL/min/kg
  - Proteinurea 0.2 g/L
- Arterial hypertension despite bitherapy
- Liver function tests: normal values
What are you proposing?

A / Tac withdrawal and monotherapy with mycophenolate

B / Dual therapy mycophenolate + everolimus

C / Switch from Tac to everolimus monotherapy

D / No change for now…

E / Low dose of Tac (target C0 3-5 ng/mL) + everolimus start
CRD after LT

CNI withdrawal and monotherapy MMF for serious CNI-induced side effects

Liver transplanted patients with patent or potential severe CNI-related side effects between October 2000 and December 2014

CNI reduction by steps of 20%-25% within 6 months

Bayesian estimation of AUC MPA (\text{AUC}_{\text{MPA}})

MMF dose adjustments to reach the optimal target window \text{AUC}_{\text{MPA}} of 45\mu g \cdot h/mL

Data collection: baseline - M12 - then each year to 5 years

Figure 3

A

\begin{align*}
\text{AST (U/L)}
\end{align*}

\begin{align*}
\text{ALT (U/L)}
\end{align*}

\begin{align*}
\text{γGT (U/L)}
\end{align*}

\begin{align*}
\text{Bilirubin (mg/dL)}
\end{align*}

p=0.025

ns

\begin{align*}
\text{eGFR (mL/kg/min±SD)}
\end{align*}

\begin{align*}
46.2±10.5 & 49.1±11.5 & 53.1±13.5
\end{align*}

Patients at risk:

\begin{align*}
n=94 & n=77 & n=13
\end{align*}

Lassaily G, et al. Submitted
# CNI minimization with antimetabolites/induction agents in de novo liver transplantation

<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>IS</th>
<th>AR</th>
<th>Renal function (eGFR*), mean</th>
<th>F-UP (mo)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boudjema et al 2011</td>
<td>Randomized controlled</td>
<td>CNI+S (#100) rCNI+MMF+S (#95)</td>
<td>46% vs. 30% (p=0.024)</td>
<td>78 ± 26 vs. 90 ± 30 (p = 0.004**)</td>
<td>12</td>
<td>rCNI+MMF+S: superior outcome of renal function and rejection rates</td>
</tr>
<tr>
<td>Benitez et al 2010</td>
<td>Randomized controlled</td>
<td>TAC+S (#16) vs. ATG+rTAC→weaning 3 mo. (#21)</td>
<td>31.2% vs. 66.7% (p=0.03)</td>
<td>NA</td>
<td>12</td>
<td>Study stopped prematurely due to ↑rejection in very-low TAC arm (&lt;5ng/mL)</td>
</tr>
<tr>
<td>Neuberger et al 2009</td>
<td>Randomized controlled</td>
<td>(A)TAC-C+S vs. (B)rTAC+MMF+S vs. (C) anti-CD25+ +drTAC+MMF+S</td>
<td>27.6% vs. 29.2% vs. 19.0%</td>
<td>eGFR decrease by 23.61 vs. 21.22 vs. 13.63 mL/min at M12 (A vs C, p=0.012; A vs. B, p=0.199)</td>
<td>12</td>
<td>Superior renal function for anti-CD25+drTAC+MMF vs. TAC-C. Non superiority of rTAC+MMF vs. TAC due to overlapping blood levels</td>
</tr>
<tr>
<td>Nashan et al 2009</td>
<td>Randomized controlled</td>
<td>sTAC+MMF+S + (#28) vs. rTAC+MMF+S (#27)</td>
<td>17.8% vs. 18.5%</td>
<td>CrCl 66.3 (17.6-110.2) 78.6 (49.6-172.8)</td>
<td>6</td>
<td>Comparable efficacy</td>
</tr>
</tbody>
</table>

AR: acute rejection; ATG: anti-thymocyte globulin; CNI: calcineurin inhibitor; CNI-C: CNI control; CsA: cyclosporin; dCNI: delayed CNI; drCNI: delayed-reduced CNI; dTAC: delayed TAC; EVR: everolimus; F-UP: follow-up; IS: immunosuppression; MMF: mycophenolate mofetil; rCNI: reduced CNI; rTAC: reduced TAC; sTAC: standard TAC; S: steroids; SRL: sirolimus; TAC: tacrolimus; TAC-C: TAC control
# CNI minimization with antimetabolites/induction agents in de novo liver transplantation

<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>IS</th>
<th>AR</th>
<th>Renal function (eGFR*), mean</th>
<th>F-UP (mo)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Otero A et al 2009</td>
<td>Randomized controlled</td>
<td>TAC+S (#79) vs. antiCD25+TAC+MMF+S (#78)</td>
<td>26.6% vs. 11.5% (p=0.017)</td>
<td>sCr (mg/dL) 1.2 vs. 1.0</td>
<td>6</td>
<td>Overlapping between arms for TAC levels</td>
</tr>
<tr>
<td>Bajjoka et al 2008</td>
<td>Retrospective cohort</td>
<td>CNI+MMF+S (#80) vs. ATG+dCNI+MMF+S</td>
<td>26% vs. 16% (p=0.08)</td>
<td>43.7 vs. 57.4 (p&lt;0.001)</td>
<td>12</td>
<td>ATG induction with delayed CNI: lower incidence of early acute rejection and superior renal function</td>
</tr>
<tr>
<td>Lin et al 2005</td>
<td>Non-randomized controlled</td>
<td>TAC+S (#18) vs. BAX+rTAC+S (#27)</td>
<td>27.8% vs. 11.1 (p=ns)</td>
<td>Median CrCl at M3 57 vs. 72 mL/min (p=0.04)</td>
<td>6</td>
<td>Comparable efficacy of BAX+rTAC+S vs. TAC+S</td>
</tr>
<tr>
<td>Yoshida et al 2005</td>
<td>Randomized controlled</td>
<td>CNI+MMF+S (#76) vs. antiCD25+drCNI+MMF+S</td>
<td>27.7% vs. 23.2% (p=0.68)</td>
<td>69.5 vs. 75.4 (p=0.038) at 6 mo. 73.2 vs. 71.7 (p=0.587) at 12 mo.</td>
<td>12</td>
<td>Superior renal function under delayed rCNI only in the early post-transplant period</td>
</tr>
</tbody>
</table>

AR: acute rejection; ATG: anti-thymocyte globulin; BAX: basiliximab; CNI: calcineurin inhibitor; CNI-C: CNI control; CsA: cyclosporin; dCNI: delayed CNI; drCNI: delayed-reduced CNI; dTAC: delayed TAC; EVR: everolimus; F-UP: follow-up; IS: immunosuppression; MMF: mycophenolate mofetil; rCNI: reduced CNI; rTAC: reduced TAC; S: steroids; SRL: sirolimus; TAC: tacrolimus; TAC-C: TAC control.
EVR + rTAC after liver transplantation: the H2304 study design

A multicenter, open-label, randomized, controlled study to evaluate the efficacy and safety of EVR to eliminate or reduce TAC in *de novo* liver transplant recipients

**TAC Elimination halted early due to high AR rate**

**EVR + Reduced TAC**
- EVR C0 3–8 ng/mL
- TAC C0 3–5 ng/mL

**TAC Control**
- TAC C0 8–12 → ↓ 6–10 ng/mL (M4)

**All: TAC/CS ± MMF (BL-D30)**

<table>
<thead>
<tr>
<th>M1</th>
<th>M4</th>
<th>M6</th>
</tr>
</thead>
<tbody>
<tr>
<td>± CS after M6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Enrollment into TAC-WD arm was stopped due to higher rejection rates and protocol was amended based on DMC recommendation (Apr 2010)

Clear separation and clinically relevant reduction in TAC exposure in EVR + rTAC arm

![Graph showing reduction of TAC C0 levels in EVR + rTAC vs TAC-C (%)]

Renal function in patients on EVR + reduced TAC

Mean eGFR (MDRD4) [mL/min]

EVR+rTAC (n=245)  TAC-C (n=243)

Time after liver transplant (months)

What are you proposing?

A / Tac withdrawal and monotherapy with mycophenolate

B / Dual therapy mycophenolate + everolimus

C / Switch from Tac to everolimus monotherapy

D / No change for now…

E / Low dose of Tac (target C0 3-5 ng/mL) + everolimus start
Lower risk of serious cardio-vascular events on EVR + reduced TAC

Cumulative incidence of the first serious CV event

- EVL + rTAC
- EVL + eTAC
- TAC control

Bernhardt P, Suisse, ILTS 2016, Abs. O-07
Clinical observation (3)

- In February 2014: mandibular pain
- Oto-rhino-laryngology assessment: Endobuccal epidermoid carcinoma reaching the mandibular region
- Head - Neck Oncology committee:
  - Surgery (pelvimandibulectomy with lymphadenectomy under temporary tracheostomy)
  - Adjuvant radiotherapy.
- IS : Tac and MMF...
What is your management with IS?

A / Tac withdrawal and monotherapy with mycophenolate
B / Dual therapy mycophenolate + everolimus
C / Switch from Tac to everolimus now
D / Switch to everolimus one month after surgery
E / No change for now…
F / Sparing strategy with Tac to target C0 5-8 ng/mL
My management would be…

A / Tac withdrawal and monotherapy with mycophenolate

B / Dual therapy mycophenolate + everolimus

C / Switch from Tac to everolimus now

D / Switch to everolimus one month after surgery

E / No change for now…

F / Sparing strategy with Tac to target C0 5-8 ng/mL
Why not?

A / Tac withdrawal and monotherapy with mycophenolate
B / Dual therapy mycophenolate + everolimus
C / Switch from Tac to everolimus now
D / Switch to everolimus one month after surgery
E / No change for now…
F / Sparing strategy with Tac to target C0 5-8 ng/mL
Blocking mTOR inhibits protein synthesis, cell cycle transition and restores apoptosis

**RAPAMYCIN DERIVATIVES**

CCI779 = temsirolimus (Torisel→)
RAD001 = everolimus (Afinitor→)
AP23573 = deforolimus

PROTEIN SYNTHESIS
G1-S TRANSITION
APOPTOSIS
mTOR Inhibitors in recipients with de novo cancer

Use of Everolimus as a Rescue Immunosuppressive Therapy in Liver Transplant Patients With Neoplasms

Judith Gomez-Camarero, Magdalena Salcedo, Diego Rincon, Oreste Lo Iacono, Cristina Ripoll, Ana Hernando, Cecilia Sanz, Gerardo Clemente, and Rafael Bañares

Transplantation 2007

- 10 patients with SOT after LT
- Historical control without EVL

VS

Median survival 21.3 vs 5.3 months
Conversion to everolimus dramatically improves the prognosis of de novo malignancies after liver transplantation for alcoholic liver disease

- Retrospective study
- De novo SOT after LT for ALD
- 83 patients: 38 pts EVR
- EVR:
  - One year survival 77.4% vs 47.2%
  - 5 years survival 35.2% vs 19.4%
  - \( p = 0.003 \)
  - RR 0.447

Thimonier E, Clin Transpl 2014

\( p = 0.003 \)
Conversion to everolimus dramatically improves the prognosis of de novo malignancies after liver transplantation for alcoholic liver liver disease.

Metastatic (N+M+)

1Y: 62.5 vs 11.1 %
Basical-Pivotal IS regimen for ALD
Synergistic action

Before 6 months

CNI

MPA

Steroids
Basical-Pivotal IS regimen for ALD
Synergistic action

Before 6 months

CNI

MPA

Steroids

After 6 months

CNI

MPA
The modern trend in high risk *de novo* SOT

During 1st months
The modern trend in high risk *de novo* SOT

**During 1st months**

- CNI
- MPA
- IL2r mAb
- Steroids

**After x months**

- mTORi
- CNI
Clinical observation (4)

- EVL initiation after surgery 0.75 mg x 2/jr
- Mycophenolate withdrawal
- Tapering use of Tac
- At the end 2016: metastatic lung progression
- Systemic chemotherapy by ERBITUX and TAXOL
- Reduced EVL C0 level < 5
- Death in October 2017
Conclusions

1) Patients take benefit from CNI sparing strategies reducing:
   - *De novo* solid cancers
   - HCC recurrence
   - Serious cardio vascular events
   - Chronic renal dysfonction

2) However few patients may develop humoral rejection (AMR)

3) Interest to develop new tools to individualize management of IS minimization and to identify « High risk patients »
Management of liver recipients

Vilfredo Pareto (1848–1923)
Italian sociologist, economist and philosopher.
He made several important contributions to economics,
particularly in the study of income distribution and in the
analysis of individuals' choices

Pareto principle
« 80% of effects are the products of 20% of causes »

Most of the concerns are concentrated in few patients!
BACK UP
What about Donor-specific antibody (DSA) after minimization?

The Need for precision

- Timing
  - Preformed (retransplantation, female recipient, transfusion, biliary or autoimmune disease)
  - De novo

- Specificity
  - Class II: mostly preformed
    - DSA (impact of DQ ++)
  - Class I: mostly de novo, persisting

- Quantification
  - Quantified by Luminex +++ (Mean Fluorescence Intensity – MFI): positive > 300-500
  - Considered high when > 10,000

- Persistence
  - Yes
  - No

Question: What about Donor-specific antibody (DSA) after minimization?
De novo DSA after liver transplantation
Controversial impact

De Novo Donor-Specific HLA Antibodies Decrease Patient and Graft Survival in Liver Transplant Recipients

H. Kaneku1,*, J. G. O’Leary2, N. Banuelos3, L. W. Jennings3, B. M. Susskind3, G. B. Klintmalm7 and P. I. Terasaki1,3

Received 02 November 2012, revised 16 January 2013 and accepted 04 February 2013

De novo DSA HR 1.99
Low CNI level
Impact on de novo DSA development

<table>
<thead>
<tr>
<th>Immunosuppression</th>
<th>DSA−</th>
<th>DSA+</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Induction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>73%</td>
<td>42%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>62%</td>
<td>60%</td>
<td>0.50</td>
</tr>
<tr>
<td>Rapamycin</td>
<td>16%</td>
<td>29%</td>
<td>0.20</td>
</tr>
<tr>
<td>Steroids</td>
<td>40%</td>
<td>18%</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>HLA mismatches (total)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 DQ HLA mismatches</td>
<td>6 (5–7)</td>
<td>7 (6–8)</td>
<td>0.07</td>
</tr>
<tr>
<td>Antibody characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class II preformed</td>
<td>0%</td>
<td>22%</td>
<td>0.001</td>
</tr>
<tr>
<td>Class II de novo</td>
<td>0%</td>
<td>82%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cyclosporine (compared to tacrolimus) at 1 year</strong></td>
<td>2.61</td>
<td>1.48–4.62</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sirolimus at 1 year</td>
<td>1.83</td>
<td>0.99–3.4</td>
<td>0.055</td>
</tr>
<tr>
<td>Steroids at 1 year</td>
<td>0.51</td>
<td>0.28–0.9</td>
<td>0.021</td>
</tr>
<tr>
<td>Mycophenolate vs Azathioprine/none at 1 year</td>
<td>1.07</td>
<td>0.63–1.81</td>
<td>0.805</td>
</tr>
<tr>
<td>Low level of calcineurin inhibitor in the first year</td>
<td>2.3</td>
<td>1.14–4.66</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Univariate analysis vs Multivariable analysis

Kaneku, AJT, 2013
O’Leary, AJT, 2016
mTOR inhibitors and DSA

Evolution of donor-specific antibodies (DSA) and incidence of de novo DSA in solid organ transplant recipients after switch to everolimus alone or associated with low dose of calcineurin inhibitors

<table>
<thead>
<tr>
<th></th>
<th>EVR+</th>
<th>EVR−</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASMR (%)</td>
<td>2 (3.3)</td>
<td>4 (5.5)</td>
<td>NS</td>
</tr>
<tr>
<td>ACR (%)</td>
<td>6 (10.1)</td>
<td>7 (9.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Time from switch to ACR (months)</td>
<td>Not relevant</td>
<td>Not relevant</td>
<td>NS</td>
</tr>
<tr>
<td>Time from switch to ASMR (months)</td>
<td>1-2</td>
<td>Not relevant</td>
<td>NS</td>
</tr>
<tr>
<td>Pre-transplantation anti-HLA antibodies (%)</td>
<td>8 (15.5)</td>
<td>13 (18)</td>
<td>NS</td>
</tr>
<tr>
<td>DSA before transplantation (%)</td>
<td>2 (3.3)</td>
<td>7 (8.7)</td>
<td>NS</td>
</tr>
<tr>
<td>DSA before conversion to EVR (%)</td>
<td>9 (18.9)</td>
<td>15 (20.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Number of de novo DSA after switch (%)</td>
<td>4 (6.7)</td>
<td>8 (11.1)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Class I de novo DSA

<table>
<thead>
<tr>
<th></th>
<th>EVR+</th>
<th>EVR−</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (number)</td>
<td>2</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>DSA (number)</td>
<td>4</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>MFI immunodominant (median)</td>
<td>3180 ± 1008.8</td>
<td>2214 ± 1350.37</td>
<td>NS</td>
</tr>
</tbody>
</table>

Class II de novo DSA

<table>
<thead>
<tr>
<th></th>
<th>EVR+</th>
<th>EVR−</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (number)</td>
<td>2</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>DSA (number)</td>
<td>2</td>
<td>12</td>
<td>NS</td>
</tr>
<tr>
<td>MFI immunodominant (median)</td>
<td>3274 ± 1103.2</td>
<td>3380 ± 3351.6</td>
<td>NS</td>
</tr>
</tbody>
</table>

Progression of de novo DSA MFI sum from M9 to M12

<table>
<thead>
<tr>
<th>Class I</th>
<th>Class II</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Mean delay from switch to DSA de novo detection (months)</td>
<td>9 ± 3.8</td>
</tr>
<tr>
<td>Median (range) of DSA number after switch</td>
<td>2 (1-6)</td>
</tr>
</tbody>
</table>
Antibody-mediated rejection
Take home messages

• AMR is a reality
  – Acute AMR: high sensitized recipients
  – Chronic AMR: IS minimization

• Crossmatch T/B, HLA DSA monitoring
• Liver graft biopsy protocol
• To define therapeutic protocol