Immunesuppression in Liver Transplantation: More, Less or None

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Educational Goals

• Discuss IS in the present setting (How much?)
  • Benefits
  • Limitations

• Review IS withdrawal (None?)
  • Spontaneous
  • Induced
LT Current challenges to long term survival

• Long term mortality (1y post LT)
  • Hepatic causes 28%
  • Malignancy 22%
  • Cardiovascular 11%
  • Infections 9%
  • Renal Failure 6%

Watt et al. AJT 2010
Long term mortality post LT

Watt et al. AJT 2010
Modifiable Factors

- DM
- Hypertension
- Obesity
- Frailty
- Renal Insufficiency
- Smoking
Modifiable Factors

- DM 15%-25% 1y, 33% overall
- Hypertension 17%-56% 1y, 67% overall
- Renal Insufficiency 17%, 47% overall
- Hemodialysis 6% at LT, 10% overall
- Smoking 46%

Watt et al. AJT 2010
Cause specific probability of death over time

Watt et al. AJT 2010
Renal Failure: A very special problem

- Time dependent multivariable analysis showed
  - Renal failure increased mortality HR in
    - Overall deaths beyond 1y **3.59** (2.50-5.16)
    - Liver related deaths beyond 1y **5.10** (2.41-10.8)
    - Malignancy deaths beyond 1y **2.66** (1.35-5.25)

And timing is everything

- If renal failure occurred 1-5 y post LT
  - HR for all cause mortality **2.73** (1.56-5.69)

Watt *et al.* AJT 2010
IS then is the **major** modifiable denominator

- IS will impact:
  - HTN
  - CyA
  - DM
    - Steroids
    - Tacrolimus
  - Hyperlipidemia
    - mTOR inhibitors
  - Most importantly, **renal function** is affected
  - CyA and tacrolimus
LT: from then to now

- Current results in LT are due to
  - Excellent IS in an organ that is tolerant
  - Improved patient selection
    - Better control of primary disease
  - Clinical care
    - Surgical
    - Intensive care
    - Post-operative medical care
Liver Transplant IS milestones

- Pre-1978 steroids and azathioprine
- CyA IS properties discovered in 1976
  - approved for clinical use 1983
- Tacrolimus (1994) and mycophenolate (1995)
- Monoclonal Ab’s became more available later
  - Dacluzumab 1997
  - Basiliximab 1998
  - Alemtuzumab 2001
- 2000’s mTOR inhibitors
  - Sirolimus 2001
  - Everolimus 2009
And the graft survival has improved…
Graft failure rate

Kim et al  AJT 2014
Liver Transplant Rates: *Still flat*

Kim et al AJT 2016
Survivors by Age at LT

Kim et al  AJT 2014
Incidence of ACR

Kim et al  AJT 2014
A Clinician’s Approach

• Patients have benefited from IS over time

• Minimal IS after first year should be a unifying goal

• Renal insufficiency is primary target

• Malignancy, hypertension and hyperlipidemia also important
  • More so as NASH and ASH likely to be fast growing group
Current Strategies on IS

• Steroids
  • Most centers **decrease** steroids gradually and D/C by 4-6 months post LT
  • Exceptions are pts who have AIH (pre-LT or de novo)
  • Use in ACR is generally limited to pts with high Banff scores and most centers limit to BPAR
  • This strategy improves DM, osteopenia and CV disease. May also limit infectious complications
Current Strategies on IS

- Calcineurin inhibitors
  - Tacrolimus by far most common
    - Has led to very low chronic rejection (5%)
  - Uniform desire to reduce to trough levels between 5-7 ng/dL in the first year
    - This decreases renal toxicity
    - Improves neurological side effects
    - May decrease NODAT
  - Tacrolimus “rescue” for BPAR with low Banff and for chronic rejection
Current Strategies on IS

• Calcineurin inhibitors

• Most centers begin treatment with mycophenolate

• While there are many patients who can be managed with CI regimen alone, MMF is used to decrease levels of CI
  • Kidney sparing CI/MMF approach
Current Strategies on IS

• mTOR inhibitors
  • Had wide appeal due to renal sparing profile
  • Price paid was higher ACR rate and discontinuation due to lipid profile
  • Sirolimus associated with HA throbosis (perhaps unfairly)
  • Ulceration, poor wound healing and edema make them less appealing to pts
Current Strategies on IS

- mTOR inhibitors
  - The use of these agents with MMF or combined with lower doses of CI have been adopted by many centers
  - Increased ACR and lipid management have to be weighed when deciding if needed
  - May be potentially anti neoplastic so appeals in setting of HCC or CCA complicated cases IS
Current Strategies on IS

• Induction therapies
  • Many centers used induction to diminish the impact to kidneys of early CI
  • Became very popular during the transition to MELD when significant numbers of pts with renal failure were favored for LT
  • ATG, basiliximab and daclizumab were heavily used
  • Alemtuzumab did not appeal to the field due to negative impact on HCV
How we use them currently

Kim et al  AJT 2014
Overall Approach

• When managing IS post LT, imperative to:
  • Consider comorbidities
  • Inculcate sense of responsibility to minimize risk of ACR but avoid over-treating patients as the consequences are dire
  • Renal function should be monitored and protected at all costs
  • DM, hypertension, dyslipidemia should not be ignored
The answer about how much:

• A resounding LESS
  • Soon and focus on renal function always
Can IS be eliminated?

• The resounding answer appears to be yes, in some

• The concept revolves around tolerance a concept that so far has been very favorable in liver transplantation

• Unfortunately, we have made small strides in the development of strategies to maximize tolerance
Hepatic immunology

- Unique hepatic conditions:
  - Donor specific immune-regulatory effects
  - Clonal deletion of alloreactive cells
  - Presence of APC (dendritic cells/Kupffer cells) that modulate and blunt recipient response
  - Alloantibody inhibition or dilution
  - Donor-receipient hematopoetic chimerism

- Combined effect is blunting of innate and adaptive immunity in proportion of LT recipients
Rejection and its risk in LT

- The liver is generally considered very tolerant to rejection.
- For clinical LT, rejection is usually an acute rejection, very rarely hyperacute (except when jumping ABO groups).
- ACR is generally a *direct* pathway (donor APC to recipient T cell) and innate in nature.
- Although presence of DSA are reported, often not a factor in clinical management.
Rejection and its risk in LT

• The ACR mechanism is predominantly reflexive and direct, without the need of processing allogeneic antigens

• More indirect processes appear to lead to chronic rejection but may also be the reason the liver is tolerant of rejection

• Several hepatic cells, but particularly dendritic cells can present antigens and activate lymphocytes
  • Resulting response is blunted and may promote tolerance
ACR

- Should be considered an *early event* (5-10 days post LT) and because it responds nicely, confirmed with biopsy and treated
  - Acute rejection occurring later in the course of LT more likely represents recipient immune reaction and may herald poor compliance

- Confirm histologically and monitor pt closely, could lead to chronic rejection
Chronic Rejection

• Very rare in LT (5%)

• Generally a duct-directed reaction occurring in poorly compliant pts or those who had unrecognized DSA-driven rejection

• May present as alloimmune hepatitis (like AIH) or vague non-specific hepatitis long post LT

• Management usually involves increasing tacrolimus doses
Tolerance

• As the name implies, tolerance is defined as non-reactivity to specific antigens, while still having functional immunity in IS setting

• Operational Tolerance is a situation where transplanted graft is clinically stable off IS

• Clinical trials/series have looked at spontaneous and induced operational tolerance
### Published Immunosuppression Withdrawal Studies

<table>
<thead>
<tr>
<th>Center patients</th>
<th>Adult or Pediatric</th>
<th>DOLT or LDLT</th>
<th>Age at LT (years)</th>
<th>LT Time</th>
<th>Time from LT to Weaning (years)</th>
<th>Tolerant*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pittsburgh (n=95)</td>
<td>Both</td>
<td>DOLT</td>
<td>-</td>
<td>Mean 8.4 ± 4.7</td>
<td>18 (18.9%)</td>
<td></td>
</tr>
<tr>
<td>London (n=18)</td>
<td>Adult</td>
<td>DOLT</td>
<td>Mean 57</td>
<td>Median 7 (5-11)</td>
<td>5 (27.9%); 10-year: 2 (11%)</td>
<td></td>
</tr>
<tr>
<td>Kyoto (n=115)</td>
<td>Pediatric</td>
<td>LDLT</td>
<td>Median 1.1 (0.1-15.2)</td>
<td>&gt;2 per protocol</td>
<td>49 (42.6%)</td>
<td></td>
</tr>
<tr>
<td>Murcia (n=20)</td>
<td>Adult</td>
<td>DOLT</td>
<td>Mean 47.7</td>
<td>Mean 4.9 (2.8-7.5)</td>
<td>8 (40%)</td>
<td></td>
</tr>
<tr>
<td>Rome (n=34)</td>
<td>Adult</td>
<td>DOLT</td>
<td>Mean 62</td>
<td>Mean 5.3 ± 1.7</td>
<td>8 (23.5%); 6.5-year: 7 (20.5%)</td>
<td></td>
</tr>
<tr>
<td>New Orleans (n=18)</td>
<td>Adult</td>
<td>DOLT</td>
<td>-</td>
<td>&gt;0.5 per protocol</td>
<td>1 (5.6%)</td>
<td></td>
</tr>
<tr>
<td>Winnipeg (n=25)</td>
<td>Adult</td>
<td>DOLT</td>
<td>Mean 53.7</td>
<td>Mean 4.6</td>
<td>2 (7.6%)</td>
<td></td>
</tr>
<tr>
<td>Miami (n=104)</td>
<td>Adult</td>
<td>DOLT</td>
<td>Mean 49.5</td>
<td>Mean 4.07</td>
<td>20 (19.2%); 10-year: 16 (15.4%)</td>
<td></td>
</tr>
<tr>
<td>San Francisco (n=20)</td>
<td>Pediatric</td>
<td>LDLT</td>
<td>Median 0.6 (0.3-7.2)</td>
<td>Median 8.5 (5.0-15.3)</td>
<td>12 (60%)</td>
<td></td>
</tr>
<tr>
<td>Barcelona (n=102)</td>
<td>Adult</td>
<td>DOLT</td>
<td>Mean 47 ± 10</td>
<td>Mean 8.7 ± 3.9</td>
<td>41 (40.2%)</td>
<td></td>
</tr>
<tr>
<td>Pamplona (n=24)</td>
<td>Adult</td>
<td>DOLT</td>
<td>-</td>
<td>Median (interquartile range 6-13.3)</td>
<td>15 (62.5%)</td>
<td></td>
</tr>
<tr>
<td>Taiwan (n=16)</td>
<td>Pediatric</td>
<td>Both</td>
<td>Mean 4.0 ± 4.8</td>
<td>7.8 ± 5.4</td>
<td>5 (31.3%)</td>
<td></td>
</tr>
<tr>
<td>Sapporo (n=10)</td>
<td>Adult</td>
<td>LDLT</td>
<td>-</td>
<td>&gt;0.5 per protocol</td>
<td>7 (70%)</td>
<td></td>
</tr>
</tbody>
</table>
Tolerance in pediatric patients

- WISP-R trial in San Francisco/NYC/Chicago
- 20 children, all LDLT recipients, >4yr from LT
- Normal baseline liver function and biopsy
- Gradually D/C IS over 36 months
- Operational tolerance 12mo IS free with normal graft

Feng et al.
JAMA 2012
WISP-R

- 12/20 patients became tolerant spontaneously
- Liver biopsy at 1 and 5 years now have shown no evidence of progressive graft damage, no rejection episodes, no graft losses
- Long term follow up demonstrated maintenance of DSA in those where they pre-existed and several de novo DSA generation

Feng et al.
JAMA 2012
WISP-R

- In pediatric patients, well selected candidates can be weaned off IS
- The parameters needed to select those patients are the subject of a second trial, soon to be completed, the iWITH trial, now with larger pool of pediatric patients

Feng et al. JAMA 2012
What about the adults?

• The Barcelona group has convincingly shown that in well selected adult cohorts Spontaneous OT occurs as well

• Their study included 102 patients who had been post-LT at least 3 yrs, and who had stable liver function and biopsy

• 41/102 were sOT per the protocol

Benitez et al.  
Hepatology 2013
What about the adults?

- The most compelling information from a practical standpoint is that pt age at LT and time post LT were pivotal in selecting responders.

- Older donors > 50yrs and transplanted 5-10 yr prior to weaning are those most likely to respond favorably to IS withdrawal.

- ACR in this setting was mild and responsive to treatment.

Benitez et al. Hepatology 2013
What about the adults?
Likelihood of freedom from rejection

Benitez et al.
Hepatology 2013
What about the adults?
Now factor in age and duration of LT

Benitez et al.
Hepatology 20
What is next in this area

- Two large, international trials will be launched that have as a hallmark the test of biomarkers that identify those patients likely to have sOT

- One in US will look for evidence of IS senescence as a marker of tolerance (OPTIMAL)

- One in Europe will look at biomarker panels that will be help identify those with sOT vs. undifferentiated withdrawal (LIFT)
Induced OT with T-Cell Based Cell Therapy

- Pilot study carried out in Japan
- 10 LDLT recipients received ex vivo generated Treg cells.
- Cells were generated in co-culture of recipient lymphocytes with irradiated donor cells in presence of CD80/86 monoclonal Abs

Todo et al. Hepatology 2016
Induced OT with T-Cell Based Cell Therapy

- Donor cells were obtained before transplantation
- Recipient cells were obtained 1 day pre LDLT
- Spleen was harvested and lymphocytes obtained as well
- Infusion occurred at day 13 post-op

Todo et al. Hepatology 2016
Treatment Scheme

Todo et al. Hepatology 2016
Clinical Results

- 7/10 patients completely off IS > 1000d post LT
- ACR cases were mild
- No graft loses
- All pts have good graft function
- Although small encouraging

Todo et al. Hepatology 2016
So do we stop IS?

• The answer is yes
• But is important how
  • Currently we rely on sOT
  • We need to understand who will be able to stop
    • Age
    • Duration of engraftment very important
• In future, we may be able to select who stops
• Or better yet, induce.