Immunesuppression in LT: Can it be done a la carte?

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Educational Goals

• Discuss IS in the present setting
  • Benefits
  • Limitations
  • Specific Strategies

• Review IS withdrawal
  • 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% 67% overall
- Renal Insufficiency 17%-47% overall
- Hemodialysis 6% at LT, 10% overall
- Smoking 46% o

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 focus

• 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
How we use them currently

Kim et al AJT 2014
And the graft survival has improved…

Graft failure rate

Kim et al  AJT 2014
Liver Transplant Rates

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 prevention 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

- Renal sparing strategies
- Most centers begin treatment with mycophenolate
- IL-2 receptor induction and hold steroids 3-5d
- 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 some centers
  - Increased ACR and lipid management costs 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 sig 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
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
Can IS be eliminated?

- The resounding answer appears to be yes, in some cases.

- The concept revolves around tolerance, a concept that so far has been very fortunate 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/Kuppfer cells) that modulate and blunt recipient response
  • Alloantibody inhibition or dilution
  • Donor-receipient hematopoietic 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 unusually 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, most 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 have looked at spontaneous and induced operational tolerance
## Published Immunosuppression Withdrawal Studies

<table>
<thead>
<tr>
<th>Center (n)</th>
<th>Adult or Pediatric</th>
<th>DOLT or LDLT</th>
<th>Age (years)</th>
<th>LT Time</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>
</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 (27.8%); 10-year: 2 (11%)</td>
</tr>
<tr>
<td>Kyoto (n=115)</td>
<td>Pediatric</td>
<td>LDLT</td>
<td>Median 0.1-15.2</td>
<td>&gt;2 per protocol</td>
<td>49 (42.6%)</td>
</tr>
<tr>
<td>Murcia (n=20)</td>
<td>Adult</td>
<td>DOLT</td>
<td>Mean 47.7</td>
<td>Mean 4.9 (2-8.75)</td>
<td>8 (40%)</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>
</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>
</tr>
<tr>
<td>Winnipeg (n=26)</td>
<td>Adult</td>
<td>DOLT</td>
<td>Mean 53.7</td>
<td>Mean 4.6</td>
<td>2 (7.6%)</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>
</tr>
<tr>
<td>San Francisco (n=20)</td>
<td>Pediatric</td>
<td>LDLT</td>
<td>Median 0.3-7.2</td>
<td>Median 8.5 (5.0-15.3)</td>
<td>12 (60%)</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>
</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>
</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>
</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>
</tr>
</tbody>
</table>
Tolerance in pediatric patients

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

Hepatology. 2017 Feb;65(2):647-660
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

Hepatology. 2017 Feb;65(2):647-660
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

Hepatology. 2017 Feb;65(2):647-660
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
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.

Hepatology 2013 58  1824–1835
What about the adults?  
Likelihood of freedom from rejection
What about the adults?
Now factor in age and duration of LT

Hepatology 2013 58 1824–1835
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
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
Treatment Scheme

- Day 5: Cyclophosphamide (40 mg/kg)
- Day 13: Cell infusion
- Steroid (MPSE): 20 mg/d
- MMF: 500-1500 mg/d
- CNI (Tacrolimus / Cyclosporine)

Twiced daily: 0, 1M, 6M, 9M, 12M, 15M, 18M
Once daily: 0, 1M, 6M, 9M, 12M, 15M, 18M
x3/wk: 0, 1M, 6M, 9M, 12M, 15M, 18M
x2/wk: 0, 1M, 6M, 9M, 12M, 15M, 18M
x1/wk: 0, 1M, 6M, 9M, 12M, 15M, 18M

IS off: 18M
Clinical Results

- 7/10 patients completely off IS > 1000d post LT
- ACR cases were mild
- No graft loses
- All pts have good graft function
What is next in this area

- Two large, international trials will give information hallmark the test of biomarkers that identify those patients likely to have s OT


- One in Europe will look at biomarker panels that will be help identify those with potential for OT vs. undifferentiated withdrawal (LIFT) https://www.clinicaltrials.gov/ct2/show/NCT02498977.