LTBI Treatment in non–HIV immunosuppressed patients

Richard Zuckerman, MD, MPH, FIDSA
Disclosures

- AiCuris, Medpace – DSMB for acyclovir-resistant HSV
Case

• 67 yo M with cirrhosis due to NASH, hepatocellular carcinoma undergoing treatment. Frequent paracenteses. LFT’s fluctuate.

• Currently in active workup for liver transplant.
  • Positive IGRA, direct exposure to uncle with TB as a child.

• Should you give LTBI treatment?
  • What do you give and when?
Outline

• Review epidemiology of TB risk
  • Solid Organ Transplant (SOT)
  • Biological drugs (biologics)
  • Hematopoietic Stem Cell Transplant (HSCT)
• No discussion about diagnosis
• LTBI therapy
  • SOT
    • Organ disease, medication interactions
  • Non-SOT
    • Biologics
    • HSCT
    • Donors
• Future therapeutic possibilities
Global activity in organ transplantation

<table>
<thead>
<tr>
<th>Organ Type</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>89,823</td>
</tr>
<tr>
<td>Liver</td>
<td>30,352</td>
</tr>
<tr>
<td>Heart</td>
<td>7,626</td>
</tr>
<tr>
<td>Lung</td>
<td>5,497</td>
</tr>
<tr>
<td>Pancreas</td>
<td>2,342</td>
</tr>
<tr>
<td>S. bowel</td>
<td>220</td>
</tr>
</tbody>
</table>

≈ 135,860 solid organ transplants reported in 2016
≈ 7.25% increase vs 2015
≤ 10% of global needs
40.2% living kidney transplants
19.8% living liver transplants

Information of 110 Member States on organ transplantation activities is included in the GODT: 81 of 2016, 11 of 2015, 6 of 2014, 7 of 2013, 2 of 2012 and 3 of 2011.
What type of TB disease do we see?

• SOT recipients
  • Reactivation of latent tuberculosis - majority
  • Transmission from donor (living or cadaveric) (<5%)
  • Acquisition after transplant
  • Transplant tourism (risk 2-10%?)

• Biologics, immunosuppressives and HSCT
  • Reactivation
  • New acquisition
# Biologics that interfere with TB control

<table>
<thead>
<tr>
<th>Target</th>
<th>Cell type</th>
<th>Disease</th>
<th>Biological drug inhibiting target</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-α</td>
<td>T lymphocytes, macrophages</td>
<td>RA, JIA, Psoriasis, Crohn’s</td>
<td>Infliximab, adalimumab, golimumab, certolizumab pegol, etanercept, abatacept</td>
</tr>
<tr>
<td>IL-12/23</td>
<td>Macrophages, dendritic cells</td>
<td>Psoriasis, Crohn’s</td>
<td>Ustekinumab</td>
</tr>
<tr>
<td>IL-6</td>
<td>T lymphocytes, macrophages</td>
<td>RA, GCA, JIA, CRS (CAR-T), MCCD</td>
<td>Tocilizumab, siltuximab</td>
</tr>
<tr>
<td>IL-17</td>
<td>CD4 T cells</td>
<td>Psoriasis, JIA, AOSD</td>
<td>Secukinumab, ixekizumab, brodalumab</td>
</tr>
<tr>
<td>IL-1β</td>
<td>Macrophages</td>
<td>RA, JIA, hereditary autoinflammm</td>
<td>Canakinumab, anakinra, rilonacept, gevokizumab</td>
</tr>
<tr>
<td>CD80/86</td>
<td>T lymphocytes</td>
<td>SOT</td>
<td>Betalacept (co-stim blockade)</td>
</tr>
<tr>
<td>CD52</td>
<td>lymphocytes</td>
<td>SOT, CLL, HSCT</td>
<td>Alemtuzumab</td>
</tr>
<tr>
<td>various</td>
<td>T lymphocytes</td>
<td>SOT, AA, HSCT</td>
<td>ATG</td>
</tr>
</tbody>
</table>
Incidence of active tuberculosis in organ transplant recipients by transplant type.

Many cases were from other countries

4.3/100,000 in Ontario

Higher TB burden countries: 500-638/100,000 2072/100,000 in lung

*SOT, Solid Organ Transplant.
## Characteristics of TB by immunocompromised population

<table>
<thead>
<tr>
<th></th>
<th>SOT</th>
<th>Anti-TNF</th>
<th>HSCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of patients</td>
<td>0.3-12</td>
<td>1.64-2.39</td>
<td>0.8-2.86</td>
</tr>
<tr>
<td>Risks</td>
<td>Rejection, organ</td>
<td>Biologic type</td>
<td>GvHD, T-cell depl, TBI</td>
</tr>
<tr>
<td>Timing</td>
<td>6-11 months (donor earlier)</td>
<td>4-8 months</td>
<td>3-12 months</td>
</tr>
</tbody>
</table>

### Type (location)

<table>
<thead>
<tr>
<th>Type (location)</th>
<th>Pulmonary</th>
<th>Extra-pulm</th>
<th>Disseminated</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>54-60%</td>
<td>16-30%</td>
<td>16-23%</td>
<td>~20% (15% graft loss)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Up to 60%</td>
<td>~25%</td>
<td>Up to 27%</td>
</tr>
</tbody>
</table>

INH is not well tolerated in SOT

<table>
<thead>
<tr>
<th>Therapy</th>
<th>n=189</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial LTBI therapy (%)</td>
<td></td>
</tr>
<tr>
<td>Isoniazid</td>
<td>138 (73.0%)</td>
</tr>
<tr>
<td>Rifampin</td>
<td>24 (12.7%)</td>
</tr>
<tr>
<td>Other</td>
<td>27 (14.3%)</td>
</tr>
<tr>
<td>Completion of adequate therapy (%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>122 (64.5%)</td>
</tr>
<tr>
<td>No</td>
<td>67 (33.5%)</td>
</tr>
<tr>
<td>Timing of therapy (%)</td>
<td></td>
</tr>
<tr>
<td>Pretransplant</td>
<td>142 (75.1%)</td>
</tr>
<tr>
<td>Posttransplant</td>
<td>47 (24.9%)</td>
</tr>
<tr>
<td>Reason for discontinuation of therapy (%)</td>
<td></td>
</tr>
<tr>
<td>Liver enzyme elevation</td>
<td>18 (9.5%)</td>
</tr>
<tr>
<td>Nonhepatic drug toxicity</td>
<td>24 (12.7%)</td>
</tr>
<tr>
<td>Death</td>
<td>12 (6.3%)</td>
</tr>
<tr>
<td>Nonadherence</td>
<td>6 (3.2%)</td>
</tr>
<tr>
<td>Other/ unspecified</td>
<td>7 (3.7%)</td>
</tr>
</tbody>
</table>

58% Kidney
23.5% Liver
8.5% Lung
6.5% heart

- Therapy completion (64.5%)
  - All patients:
    - More likely to complete pre-transplant
      - 69% vs. 51%
    - Liver less likely to complete than others
      - 36.1% vs. 73.9%
  - Liver transplant:
    - More like to complete post-transplant
      - 18% pre. vs. 54% post-
  - LFT abnormality:
    - Leading to therapy d/c:
      - liver 28.3% vs. 3.5% non-liver
Tuberculosis Prophylaxis With Levofloxacin in Liver Transplant Patients Is Associated With a High Incidence of Tenosynovitis: Safety Analysis of a Multicenter Randomized Trial

Clin Infect Dis. 2015;60(11):1642-1649. © The Author 2015. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. All rights reserved
But….FQ are probably tolerated

Stanford: 44 liver Txplt patients  (V. Tien, CID 2015)

<table>
<thead>
<tr>
<th></th>
<th>Fluoroquinolone (25)</th>
<th>Isoniazid (10)</th>
<th>Rifampin (9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall treatment outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed therapy</td>
<td>16 (64%)</td>
<td>6 (60%)</td>
<td>6 (67%)</td>
</tr>
<tr>
<td>Stopped due to intolerance</td>
<td>2 (8%) -1 musc.</td>
<td>4 (40%)</td>
<td>3 (33%)</td>
</tr>
<tr>
<td>Stopped due to other reasons&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7 (28%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup> Lost to follow-up (2), delisted from transplant (2), death (1), medication error (1), preference of another transplant center where patient transferred care to (1)

Toronto: 16 year retrospective.  (AlJishi, ATC 2018)

- First-line completion (89 patients)
  - INH 52/67 (77%); 10 LFT
  - rifamycins 10/12 (83.3%); 2 LFT
  - quinolones 7/7 (100%) and 5/5 second-line

** Need more TB outcomes data!
3HP is well tolerated pre-transplant

Renal/liver/heart (2014)
- 17 patients
  - 8 Kidney, 7 Liver, 2 Heart
- Good outcomes (76% completion)
- 2 (12%) drug toxicity (no liver)
  - 1 due to Hypertension (amlodipine)

Renal Transplant (2017)

<table>
<thead>
<tr>
<th></th>
<th>3HP (N=43)</th>
<th>9H (N=110)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LFT ↑</td>
<td>0</td>
<td>6 (5%)</td>
</tr>
<tr>
<td>Stopped</td>
<td>3 (7%)</td>
<td>12 (11%)</td>
</tr>
<tr>
<td>TB dz</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Med SE, changed to INH or RIF</td>
<td>Various SE</td>
<td></td>
</tr>
</tbody>
</table>

* Watch for drug-drug interactions

**LTBI treatment in SOT**

- Monitor LFT’s every 2-4 weeks
- Hold if >2-3x ULN regardless of symptoms
- If toxicity, can switch to alternative regimen or wait until after transplant
  - Fluoroquinolone is an alternative option (Check QTc)
- High TB burden settings
  - INH for 1 year after transplant regardless of LTBI testing
  - Concern for TB drug resistance
  - FQ/EMB

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**Select regimen based on transplant timing, drug interactions, liver disease, and risk of hepatotoxicity**

<table>
<thead>
<tr>
<th>Liver disease or increased risk of hepatotoxicity</th>
<th>Possible transplant within 6 mo (or) rifamycin drug interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>No, 9H, 4R, or 3HP</td>
</tr>
<tr>
<td>Yes</td>
<td>9H with close monitoring (or) RFB x 4 mo</td>
</tr>
</tbody>
</table>

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*Note:*

- No
- 9H
- 4R
- 3HP
- INH
- RFB
- FQ
- EMB

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*References:*

- Epstein, Infect Dis Clin N Am 2018
Common transplant meds, interactions

- **Corticosteroids** – rifamycins, INH (↑steroid), FQ (tendon rupture)
- **Cyclosporin A** – rifamycins, Levofloxacin (↑CSA), QTc
- **Tacrolimus** – rifamycins, QTc
- **Rapamycin (sirolimus)/everolimus** - rifamycins
- **Mycophenolate mofetil** – rifamycins, FQ (↓MMF level)
- **Bactrim** – rifamycins
LTBI in biologics

• Follow usual guidelines for treatment regimens
  • choose based on comorbidities, urgency, drug interactions, etc.
• When to start?
  • ASAP
    • Delay immunosuppressive only to ensure patient is tolerating TB meds
• Re-treat for LTBI?
  • if high risk exposure and likelihood of progression
LTBI in HSCT

• LTBI testing difficult in pre-transplant setting
  • Consider empiric therapy in those at highest risk (epidemiology)
  • Radiographic findings can also be helpful

• Often challenging to treat pre-transplant (chemo, cytopenias)

• After transplant
  • patients are on calcineurin inhibitors +/- MMF
  • May also have GvHD (liver, gut, etc.)
  • FQ commonly used around transplant

• Timing – if unable pre-transplant, consider delay of LTBI therapy until more clinically stable post-transplant

• Med choice should be guided by risks and interactions.
Organ donor LTBI

• Consensus conference (2012)
  • Tuberculosis is one of the most common bacterial infections acquired from donors
  • Outlined general guidelines
  • Cases of TB transmission – (incl. INH resistant) from inadequately treated LTBI

• 36 cases of Donor Derived TB (DDTB) - 2018
  • Factors
    • Occurs early after transplant
    • Clinical: fever, high mortality
    • Occurs commonly in the transplanted organ
    • Check with Organ procurement org. (OPO)
      • possible cases in other recipients

• No donor derived HSCT cases reported

Morris et al. AJT 2012; Abad TID 2018
Organ donor LTBI

• Living donors (kidney, liver)
  • Screen as appropriate for population
  • Treat prior to transplant, if possible – typical regimens, washout
  • Can complete therapy after transplant (recipient and donor)
    • If completing after, avoid rifamycins due to interactions
    • No data on FQ

• Cadaveric donors
  • LTBI testing (TST, IGRA) usually not feasible
  • Determine risk if possible, chest imaging can be helpful
  • Avoid using organs from suspect active TB (can obtain GeneXpert® results prior to transplant)
  • Treat after transplant if high risk
    • Some high-incidence settings may use prophylaxis (INH)

Morris et al. AJT 2012; Abad TID 2018
Future LTBI treatment possibilities

• BRIEF-TB (ACTG 5279)
  • 1HP vs 9H in HIV
• 6 week rifapentine (NCT03474029)
• Delamanid, pretomanid, bedaquiline?
Summary

• TB incidence in immunocompromised is high
• Treat prior to immunosuppression, if possible (early testing)
  • But, OK to wait if necessary
• Choose agents based on clinical/epidemiologic factors, interactions and timing
• Monitor for toxicity, drug interactions
• Need to consider this population in design of future studies

• Case follow-up:
  • LTBI therapy was delayed until 6 months after transplant
  • He completed 9 months of INH without complications.